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(71) Applicant *(for all designated States except US)*: TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SOHDA, Takashi [JP/JP]; 27-20, Higashikanmaki 2-chome, Takatsuki-shi, Osaka 569 (JP). FUJISAWA, Yukio [JP/JP]; 1-31-104, Mikagenaka-machi 4-chome, Higashinada-ku, Kobe-shi, Hyogo 658 (JP). YASUMA, Tsuneo [JP/JP]; 20-5, Takadacho, Ibaraki-shi, Osaka 567 (JP). MIZOGUCHI, Junji [JP/JP]; 18-D75-206, Tsukumodai 5-chome, Suita-shi, Osaka 565 (JP).

(74) Agents: ASAHINA, Tadao et al.; Osaka Plant of Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

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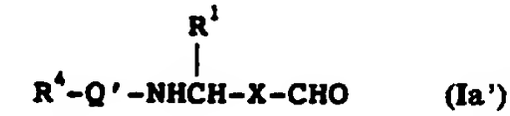
(54) Title: ALDEHYDE DERIVATIVES AS UPSTEINE PROTEASE INHIBITORS

(57) Abstract

The present invention relates to a compound of formula (Ia'), wherein Q' stands for one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optinally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxy group or an acyl group; and X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety, or a salt thereof, which has strong cysteine protease inhibitory activities and is a useful prophylactic and therapeutic agent of various diseases, including bone diseases, caused by abnormal exasperation of cysteine protease.



(Ia')

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DESCRIPTION

ALDEHYDE DERIVATIVES AS UPSTEINE PROTEASE INHIBITORS

Technical Field

This invention relates to novel acylaminoaldehyde derivatives. More specifically, it relates to novel acylaminoaldehyde derivatives showing strong inhibitory action against cysteine protease such as cathepsin L, cathepsin B and calpain.

Background Art

Recently, roles of cysteine protease, such as cathepsin L, cathepsin B or calpain (calcium-dependent neutral protease: CANP), in living bodies, and, relations of it with various diseases have come to be clarified.

For example, it has been reported that cathepsin L secreted from osteoclasts is deeply concerned with the degradation of type I collagen which is a bone supportive protein (FEBS Lett. Vol.321, p.247, 1993). Therefore, inhibition of the activity of cathepsin L, which can prevent bone collagen degradation due to bone resorption, is useful for prophylaxis and therapy of osteoporosis. And, there is a report that administration of E-64, which is an inhibitor of cathepsin L and cathepsin B, or leupeptin to rats induce a fall in the serum calcium level (Biochemical and Biophysical Research Communication, Vol.125, p.441, 1984). Therefore, inhibitors of cathepsin L and cathepsin B can be used for the therapy of hypercalcemia.

There is also a report that, in rheumatoid arthritis patients, increased cathepsin B activity has been demonstrated, and that a cathepsin B inhibitor was effective for rats suffering from adjuvant-induced arthritis, model animals of rheumatoid arthritis (Biochemical Pharmacology, Vol.44, p.1201, 1992). Thus, cathepsin B inhibitors are useful as therapeutic

agents of arthrosis such as rheumatoid arthritis or as anti-inflammatory agents.

According to another report (Tumor Progression and Markers, p.47, 1982), cathepsin B is deeply associated with the process of cancer metastasis because it participates in destruction of collagen, which is an important step of metastasis of cancer. Hence, a cathepsin B inhibitory agent is considered to be effective for suppressing the propagation of tumor cells and preventing cancer metastasis.

In the decomposition of skeletal muscle, which is observed in muscle diseases such as myodystrophy, distal myopathy and muscular atrophy, cysteine protease such as calpain or cathepsin B, is considered to play a role in the initial process, for example disappearance of Z line, through decomposition of muscular fiber protein (Shinkei Naika Chiryo, Vol. 5, p.209, 1988). Hence, an inhibitory agent of cysteine protease such as calpain or cathepsin B is considered to be effective as a therapeutic agent of myodystrophy, muscular atrophy or the like.

On senile plaques specifically observed in brains of patients suffering from Alzheimer's disease, a protein called amyloid is deposited, and this amyloid has been known to occur by the decomposition of amyloid protein precursor (APP). And, it is reported that cathepsin B is capable of degrading intact APP (Biochemical and Biophysical Research Communications, Vol.177, p.377, 1991). Therefore, a cathepsin B inhibitory agent is considered to be effective of prophylaxis and therapy of Alzheimer's disease. It is reported that an anti-cathepsin B antibody, which suppresses the action of cathepsin B, shows anti-virus activity (Japanese published unexamined patent application No. H5-105635/1993). Hence, anti-virus activity is expected also in a cathepsin B inhibitory

agent.

A cysteine protease inhibitory agent, especially an epoxysuccinic acid derivative that inhibits cathepsin B, is capable of inhibiting the activity of protease participating in processing of the immunological fragment of an antibody and suppresses the production of a specific antibody. Therefore, it can be used as a therapeutic agent of various autoimmune diseases caused by reaction of immune system with the molecule of its own, which are exemplified by rhematoid arthritis, multiple sclerosis, myathemia gravis, insulin dependent diabetes mellitus (type I diabetes mellitus), inflammatory bowl diseases, systemic lupus erythematosus, glomerulonephritis, autoimmune hemolytic anemia, Hashimoto's disease, idiopathic ulcerative colitis, primary biliary cirrhosis, idiopathic thrombocytopenic purpura, sympathetic ophthalmia, permicious anemia, Sjögren's syndrome and Goodpasture's syndrome (Japanese published unexamined patent application No. H6-336428/1994).

As described in the foregoing, abnormal increase of cysteine protease is associated with symptoms of various diseases, and some of the agents that inhibits cysteine protease are reported to be effective in experiments using, for example, an animal model.

As conventional cysteine protease inhibitory agents, epoxysuccinic derivatives such as E-64 (Agricultural and Biological Chemistry, Vol.42, p.523, 1978) and CA-074 (FEBS Lett., Vol.280, p.307, 1991), or chloromethyl ketone derivatives (Journal of Biochemistry, Vol.99, p.173, 1986) are known as irreversible inhibitors, while peptidyl aldehyde derivatives such as leupeptin (The Journal of Antibiotics, Vol. 22, p.283, 1969) are known as reversible inhibitors.

However, the above-mentioned irreversible

inhibitors are prone to be combined irreversibly with a component other than their target enzyme, and they are different from the compounds of this invention in acting mechanism.

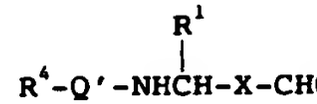
So far, there have been reports that some of α-acylaminoaldehyde derivatives have selective inhibitory activity on cathepsin L which is one of the cysteine proteases (e.g. EPC Laid-Open No.0611756A2). However, as β-, γ-, and δ-acylaminoaldehyde derivatives, although there have been reports on, for example, γ-trifluoroacetylaminoaldehydes (EPC Laid-Open No.328400A2) and γ-acetylaminoaldehyde derivatives (Bulletin of the Chemical Society of Japan, Vol.62, p.961, 1989), no disclosure on their enzyme-inhibiting activities are found at all.

Disclosure of Invention

The present inventors have diligently studied aiming at the development of novel reversible cysteine protease inhibitors which are excellent in oral absorbability and cell membrane permeability. As the result, they found that β-, γ- and δ-acylaminoaldehyde derivatives represented by the following formula (Ia) are potent reversible cysteine protease inhibitors, and have completed the present invention. So far, there have been no reports at all that acylaminoaldehyde derivatives of β-, γ- and δ-types show cysteine protease inhibitory activity. As described above, the acylaminoaldehyde derivatives of the present invention are expected to be new therapeutic medicines of various diseases in which cysteine protease plays a role.

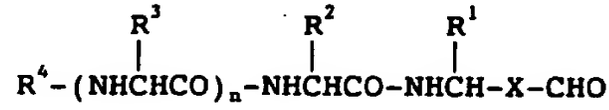
More specifically, the present invention relates to:

(1) a compound of the formula (Ia'):



wherein Q' stands for one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; and X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety, or a salt thereof,

(2) a compound of term (1) above, in which is one represented by the formula (I'):



wherein R^1, R^2 and R^3 independently stand for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety; and n is 0 or 1, or a salt thereof,

(3) a compound of term (2) above, in which R^1, R^2 and R^3 are independently an optionally substituted alkyl group,

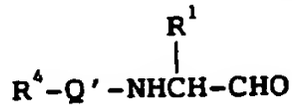
(4) a compound of term (2) above, in which R^1, R^2 and R^3 are independently a straight-chain or branched C_{1-6} alkyl group which may be substituted with an optionally substituted aryl group or a heterocyclic group,

(5) a compound of term (4) above, in which the aryl group is a phenyl group,

(6) a compound of term (4) above, in which the heterocyclic group is an aromatic heterocyclic group,

(7) a compound of term (2) above, in which R^1 is a straight-chain or branched C_{1-6} alkyl group which is

substituted with an aryl group or a heterocyclic group,
(8) a compound of term (2) above, in which R^2 and R^3 are independently a straight-chain or branched C_{1-6} alkyl group,
(9) a compound of term (2) above, in which the acyl group is that derived from a carboxylic acid, sulfonic acid, sulfinic acid, carbamic acid or thiocarbamic acid,
(10) a compound of term (2) above, in which the acyl group is represented by the formula $-SO_2R^6$ or $-COR^9$, wherein R^6 and R^9 are independently a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group,
(11) a compound of term (2) above, in which the optionally esterified carboxyl group is represented by the formula $-COOR^5$ wherein R^5 is a C_{1-6} alkyl, a C_{2-6} alkenyl or a C_{6-10} aralkyl,
(12) a compound of term (2) above, in which n is 1,
(13) a compound of term (2) above, in which n is 0,
(14) a compound of term (2) above, which is N-valproyl-(L)-valine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide, N-benzyloxycarbonyl-(L)-alanyl-(L)-alanine (1S)-3-formyl-1-benzyl-2-propenylamide, N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-(3-indolylmethyl)propylamide or N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-benzylpropylamide.
(15) a method of producing a compound of term (1) which comprises reacting a compound of the formula:

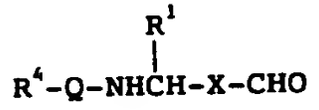


wherein Q' stands for one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; and R^4 stands for an optionally esterified carboxyl group or an acyl group, or a salt

thereof, with an acetaldehyde derivative, followed by reduction upon necessity,

(16) a composition which comprises a compound of term (1).

(17) a composition which comprises a compound of the formula (Ia):

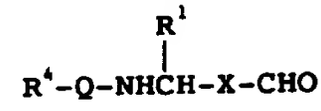


wherein Q stands for a direct bond or one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; and X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety, or a pharmaceutically acceptable salt thereof,

(18) a composition of term (17) above, which is for inhibiting a cysteine protease,

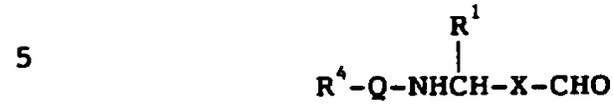
(19) a composition of term (17) above, which is for the prevention or treatment of a bone disease,

(20) a method for preventing or treating a bone disease in a mammal which comprises administering to said mammal a pharmaceutically effective amount of a compound of the formula (Ia):



wherein Q stands for a direct bond or one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; and X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a

chain length of 1 to 4 atoms as the linear moiety, or a pharmaceutically acceptable salt thereof, and
(21) use of a compound of the formula (Ia):



wherein Q stands for a direct bond or one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; and X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to be used as a cysteine protease inhibitor.

The acylaminoaldehyde derivatives in the present invention are structurally different compounds from so far known compounds having enzyme-inhibitory actions. And, among known acylaminoaldehyde derivatives such as β-, γ and δ-ones, no compounds possessing the inhibitory actions have been known. On the other hand, the compounds of the formulas (Ia') and (I') are those having a novel structure in that they have such characteristic features as showing the enzyme-inhibitory actions.

In the present specification, the constituent amino acids are of the L-configuration, unless otherwise stated. When shown by abbreviations, their notation is in accordance with the IUPAC (International Union of Pure and Applied Chemistry)-IUB (International Union of Biochemistry) Biochemical Nomenclature, e.g. Gly for glycin , Leu for leucine and Ile for isoleucine. As amino-protecting groups, those which are known in the relevant field are employed. Preferable

amino-protecting groups include acetyl, benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, tert.-butoxycarbonyl, phthalyl and formyl, with preference given to benzyloxycarbonyl or tert.-butoxycarbonyl.

With respect to the above formulas (Ia') and (Ia), the amino acid residue for the "1 or 2 amino acid residual groups which may be substituted" shown by Q' and Q, is exemplified by α-amino acids, β-amino acids and γ-amino acids, which are represented by the respective formulas $RCH(NH_2)COOH$, $H_2NCH_2CHRCO_2H$ and $H_2NCH_2CH_2CHRCO_2H$ (R represents a hydrogen atom or a hydrocarbon group or heterocyclic group which may be substituted), with preference given to α-amino acids. When Q' or Q is a dipeptidyl residue resulting from the binding of 2 amino acids, the 2 amino acids may be of the same type or not, but the residue preferably consists of 2 α-amino acids. When the dipeptidyl residue consists of 2 amino acids of the same type (e.g., amino acid residue consisting of 2 α-amino acids), the 2 amino acids may be identical or not.

The "hydrocarbon group which may be substituted" shown by R, is exemplified by the same hydrocarbon groups as those exemplifying the "hydrocarbon group which may be substituted" shown by R^1, R^2 or R^3 below.

The "heterocyclic group which may be substituted" shown by R, is exemplified by the same heterocyclic groups as those exemplifying the "heterocyclic group which may be substituted" shown by R^1, R^2 or R^3 below.

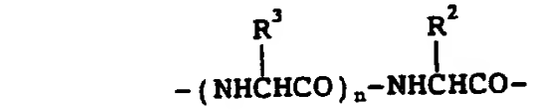
The substituent for the "hydrocarbon group or heterocyclic group which may be substituted" shown by R, is exemplified by the same substituents as those for the "hydrocarbon group or heterocyclic group which may be substituted" shown by R^1, R^2 or R^3 below.

The above described α-amino acid residue is exemplified by glycine and natural or non-natural L- or D-α-amino acids. Such amino acids include glycine, α-

L-amino acid and α-D-amino acid (.g. α-L-type or α-D-type alanine, valine, leucine, isoleucine, serin , threonine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, cysteine, methionine, phenyalanine, tyrosine, tryptophan, histidine and proline), preferably glycine, α-L-type alanine, valine, leucine, isoleucine, methionine, phenylalanine, tyrosine and tryptophan.

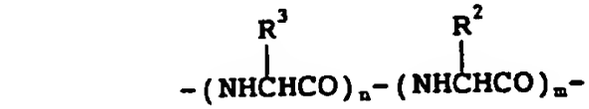
The "1 or 2 amino acid residual groups which may be substituted" shown by Q' and Q, may have 1 to 3 substituents at any possible positions. Such substituents are exemplified by the same substituents for the "hydrocarbon group or heterocyclic group which may be substituted" shown by R^1, R^2 or R^3 below.

Q' is preferably a group of the formula (Ia'-Q'):



wherein R^2 and R^3 independently stand for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; and n is 0 or 1.

Q is preferably a group of the formula (Ia-Q):



wherein R^2 and R^3 independently stand for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; and m and n independently are 0 or 1.

In the above formula, as optionally substituted hydrocarbon groups shown by R^1, R^2 or R^3, mention is made of saturated or unsaturated aliphatic hydrocarbon groups and aryl groups.

As saturat d or unsaturated aliphatic hydrocarbon groups, mention is mad of, for example, the groups set

forth in the following i) to v), namely,

i) C_{1-10} straight-chain or branched saturated aliphatic hydrocarbon groups (e.g. C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, heptyl and octyl), with preference given to C_{1-6} straight-chain or branched saturated aliphatic hydrocarbon groups,

ii) C_{2-10} straight-chain or branched unsaturated aliphatic hydrocarbon groups (e.g. C_{2-10} alkenyl groups such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl and 1-octenyl, and C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl), with preference given to C_{2-6} straight-chain or branched unsaturated aliphatic hydrocarbon groups,

iii) C_{3-12} saturated alicyclic hydrocarbon groups (e.g. C_{3-12} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl), with preference given to C_{3-6} saturated alicyclic hydrocarbon groups,

iv) C_{5-12} unsaturated alicyclic hydrocarbon groups (e.g. C_{5-12} cycloalkenyl groups such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloh pt nyl, 3-cycloheptenyl, 2,4-cycloheptadienyl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-

yl and 3-cyclohexen-1-yl, and C_{5-12} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadiene-1-yl) and

v) C_{1-8} saturated aliphatic hydrocarbon groups substituted with the above-mentioned saturated or unsaturated alicyclic hydrocarbon groups (e.g. C_{3-7} cycloalkyl-C_{1-8} alkyl or C_{5-7} cycloalkenyl-C_{1-8} alkyl, more specifically, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl, for example).

As aryl groups, mention is made of monocyclic or condensed polycyclic C_{6-14} aromatic cyclic hydrocarbon groups. Examples of the aromatic cyclic hydrocarbon groups include phenyl, tolyl, xylyl, biphenyl, 1- or 2-naphthyl, 1-, 2- or 9-anthryl, 1-, 2-, 3-, 4- or 9-phenanthryl, 1-, 2-, 4-, 5- or 6-azulenyl and acenaphthylenyl, and, among them, phenyl, 1-naphthyl and 2-naphthyl, for example, are preferable.

The "hydrocarbon group which may be substituted" shown by R^1, R^2 or R^3, may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include aryl groups that may be substituted, cycloalkyl or cycloalkenyl groups that may be substituted, heterocyclic groups that may be substituted, carboxyl groups that may be esterified, carbamoyl groups that may be substituted, amino groups that may be substituted, hydroxyl groups that may be substituted, thiol groups that may be substituted, halogens (e.g., fluorine, chlorine, bromine, iodine) and phosphono groups that may be substituted.

The "aryl group that may be substituted" is exemplified by phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl, with preference given to phenyl,

1-naphthyl and 2-naphthyl. Said aryl may have 1 to 2 optionally chosen substituents at any possible positions, these substituents including a hydroxy group, alkoxy groups that may be substituted (e.g., C_{1-3} alkoxys such as methoxy, ethoxy and propoxy), halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and alkyl groups that may be substituted (e.g., C_{1-3} alkyls such as methyl, ethyl and propyl). These alkoxy groups and alkyl groups may have 1 or 2 optionally chosen substituents at any possible positions, these substituents including phosphono groups that may be substituted (e.g., dimethoxyphosphoryl, diethoxyphosphoryl).

The "cycloalkyl group that may be substituted" is exemplified by C_{3-7} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The kinds and number of said cycloalkyl groups that may be substituted are the same as those of the substituents for the above-described aryl group that may be substituted.

The "cycloalkenyl group that may be substituted" is exemplified by C_{3-6} cycloalkenyl groups such as cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl. The kinds and number of said cycloalkenyl groups that may be substituted are the same as those of the substituents for the above-described aryl group that may be substituted.

The "heterocyclic group that may be substituted" is exemplified by aromatic heterocyclic groups having at least one hetero atom selected from atoms of oxygen, sulfur and nitrogen as a ring-constituting atom (ring atom), and saturated or unsaturated non-aromatic heterocyclic groups (aliphatic heterocyclic groups), with preference given to aromatic heterocyclic groups. Such aromatic heterocyclic groups include aromatic monocyclic heterocyclic groups (e.g., furyl, thienyl,

pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl) and aromatic condensed heterocyclic groups (e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl), with preference given to furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl etc. Such non-aromatic heterocyclic groups include oxylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperizyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazynyl. The substituent for said heterocyclic group that may be substituted is exemplified by alkyl groups having 1 to 3 carbon atoms (e.g., methyl, ethyl, propyl).

Such carboxyls that may be esterified include lower alkoxycarbonyls (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.-butoxycarbonyl, sec.-butoxycarbonyl, p ntyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, tert.-

pentyloxycarbonyl) and aryloxycarbonyls (e.g., phenoxycarbonyl, 1-naphthoxycarbonyl, benzyloxycarbonyl), with preference given to the carboxyl group, methoxycarbonyl and ethoxycarbonyl.

The substituent for said carbamoyl group that may be substituted is exemplified by lower (C_{1-6}) alkyls that may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups that may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), aryl groups that may be substituted (e.g., phenyl, 1-naphthyl, 2-naphthyl) and aralkyl groups that may be substituted (e.g., benzyl, phenethyl); 1 or 2 of these substituents, whether identical or not, may be present.

The substituent for said amino group that may be substituted is exemplified by lower (C_{1-6}) alkyls that may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups that may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), aryl groups that may be substituted (e.g., phenyl, 1-naphthyl, 2-naphthyl) and aralkyl groups that may be substituted (e.g., benzyl, phenethyl); 1 or 2 of these substituents, whether identical or not, may be present.

The substituent for said hydroxyl group that may be substituted is exemplified by lower (C_{1-6}) alkyls that may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups that may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), aryl groups that may be substitut d (e.g., phenyl, 1-naphthyl, 2-naphthyl) and aralkyl groups that may be substituted (e.g., benzyl, phenethyl).

Th substituent for said thiol group that may be substituted is exemplified by lower (C_{1-6}) alkyls that may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups that may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), aryl groups that may be substituted (e.g., phenyl, 1-naphthyl, 2-naphthyl) and aralkyl groups that may be substituted (e.g., benzyl, phenethyl).

The substituent for said phosphono group that may be substituted is exemplified by dimethoxyphosphoryl, diethoxyphosphoryl, dipropoxyphosphoryl, diisopropoxyphosphoryl, ethylenedioxyphosphoryl, trimethylenedioxyphosphoryl and tetramethylenedioxyphosphoryl.

When the "hydrocarbon group that may be substituted" shown by R^1, R^2 or R^3, is an alicyclic hydrocarbon group or an aryl group, the substituent may be an aliphatic hydrocarbon group that may be substituted. Such aliphatic hydrocarbon groups include the same saturated or unsaturated (preferably saturated) hydrocarbon groups as those exemplifying the "hydrocarbon group that may be substituted" shown by R^1, R^2 or R^3 above, with preference given to alkyl groups (e.g., C_{1-3} alkyls such as methyl, ethyl and propyl). The aliphatic hydrocarbon group may have 1 or 2 optionally chosen substituents at any possible positions, these substituents including phosphono groups that may be substituted (e.g., dimethoxyphosphoryl, diethoxyphosphoryl).

The "heterocyclic group which may be substituted" shown by R^1, R^2 or R^3, is exemplified by aromatic heterocyclic groups having at least 1 hetero atom selected from atoms of oxygen, sulfur and nitrogen as a ring-constituting atom (ring atom), and saturated or

unsaturated non-aromatic h terocyclic groups (aliphatic heterocyclic groups), with preference given to aromatic heterocyclic groups.

Such aromatic heterocyclic groups are exemplified by 5- or 6-membered aromatic heterocyclic groups containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxygen, including aromatic monocyclic heterocyclic groups (e.g. furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-pyrazinyl and triazinyl), and aromatic condensed heterocyclic groups (e.g. benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzoimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylizinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl), with preference given to furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl etc. The aromatic heterocyclic group may condense with a 6-membered ring containing 2 or fewer atoms of nitrogen, a b nzene ring, a 5-memb r d ring containing 1 atom of sulfur, or th like.

Examples of the non-aromatic heterocyclic groups include 5- to 7-membered heterocyclic groups containing one sulfur atom, nitrogen atom or oxygen atom or 5- to 6-membered heterocyclic group containing 2 to 4 nitrogen atoms, (e.g. oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, homopiperidyl, pyrrolinyl or imidazolidinyl). These non-aromatic heterocyclic groups may be such ones as being condensed with benzene ring, a 6-membered ring containing 2 or less nitrogen atoms or a 5-membered ring containing one sulfur atom. Specific examples of the condensed non-aromatic heterocyclic groups include chromanyl, isochromanyl, indolinyl, isoindolinyl, thiochromanyl or isothiochromanyl.

The "heterocyclic group that may be substituted" shown by R^1, R^2 or R^3, may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include aryl groups that may be substituted, cycloalkyl or cycloalkenyl groups that may be substituted, heterocyclic groups that may be substituted, carboxyl groups that may be esterified, carbamoyl groups that may be substituted, amino groups that may be substituted, hydroxyl groups that may be substituted, thiol groups that may be substituted, halogens (e.g., fluorine, chlorine, bromine, iodine), phosphono groups that may be substituted, and aliphatic hydrocarbon groups that may be substituted.

Said aryl groups that may be substituted, cycloalkyl or cycloalkenyl groups that may be substituted, heterocyclic groups that may be substituted, carboxyl groups that may be esterified, carbamoyl groups that may b substituted, amino groups that may be substituted, hydroxyl groups that may be substituted, thiol groups that may be substituted,

halogens (e.g., fluorine, chlorine, bromine, iodin), phosphono groups that may b substituted, and aliphatic hydrocarbon groups that may be substituted are exemplified by the same ones as substituents for the "hydrocarbon group that may be substituted" shown by R^1, R^2 or R^3 above.

Preferable examples of the optionally substituted hydrocarbon groups shown by R^1, R^2 or R^3 include the above-mentioned C_{1-10} alkyl, especially straight-chain or branched C_{1-6} lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl).

Preferable substituents for the "hydrocarbon group which may be substituted" are aryls that may be substituted (preferably phenyl etc.) and heterocyclic groups that may be substituted.

More preferably, the "hydrocarbon group which may be substituted" shown by R^1, R^2 or R^3, is an alkyl group substituted with an aryl or heterocyclic group. Said alkyl substituted with an aryl is exemplified by groups resulting from binding of a monocyclic or condensed polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl) and a lower alkyl having 1 to 6 carbon atoms (preferably C_{1-4} alkyl) (e.g., benzyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl, α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl, β-naphthylethyl). Said alkyl substituted with a heterocyclic group is exemplified by groups resulting from binding of an aromatic heterocyclic group and a lower alkyl having 1 to 6 carbon atoms (preferably C_{1-4} alkyl group). Such aromatic heterocyclic groups include 2-furyl, 3-furyl, 2-thi nyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl,

2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-2-yl, indol-3-yl, 1H-indazolyl, benz[b]furanyl, isobenzofuranyl, benz[b]thienyl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl and 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl and 1H-imidazo[4,5-b]pyrazin-2-yl, with preference given to 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-imidazolyl, 2-thienyl, 2-furyl, indol-3-yl etc.

R^1 is preferably a straight-chain or branched C_{1-6} alkyl group which may be substituted with an aryl group or a heterocyclic group (e.g., indol-3-ylmethyl, benzyl, methyl, isopropyl, 1-naphthylmethyl etc.), more preferably a straight-chain or branched C_{1-6} alkyl group which is substituted with an aryl group or a heterocyclic group.

R^2 and R^3 are preferably independently a straight-chain or branched C_{1-6} alkyl group which may be substituted with an phenyl group (e.g., sec-butyl, benzyl, isobutyl, isopropyl etc.), more prefrably independently an unsaturated straight-chain or branched C_{1-6} alkyl group.

As optionally substituted hydrocarbon groups shown by R^1, R^2 and R^3, mention is made more specifically as follows: preferable examples of R^1 include indol-3-ylmethyl, (substituted)benzyl, methyl, isopropyl and 1-naphthylmethyl; preferable examples of R^2 include sec.-butyl, benzyl, isobutyl and isopropyl; preferabl examples of R^3 include sec.-butyl, isobutyl and isopropyl.

With respect to the combination of R^1 and R^2, it is preferable that R^1 is indol-3-ylmethyl, benzyl, methyl, isopropyl or 1-naphthylmethyl and R^2 is sec.-butyl, benzyl, isobutyl isopropyl or p-hydroxyphenylmethyl.

With respect to the combination of R^1, R^2 or R^3, it is preferable that R^1 is indol-3-ylmethyl, benzyl, methyl, isopropyl or 1-naphthylmethyl, R^2 is sec.-butyl, benzyl, isobutyl or isopropyl, and R^3 be sec.-butyl, benzyl, isobutyl or isopropyl.

With respect to general formula (I), the "acyl group" shown by R^4 is exemplified by acyl groups derived from carbamic acids that may be substituted, thiocarbamic acids that may be substituted, carboxylic acids that may be substituted, sulfinic acids that may be substituted, sulfonic acids that may be substituted, etc., specifically those represented by the respective general formulas $-CONHR^7$, $-CSNHR^8$, $-COR^9$, $-SOR^{10}$, $-SO_2R^6$ (R^7, R^8, R^9, R^{10} and R^6, whether identical or not, independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted) etc.

The "hydrocarbon group that may be substituted" shown by R^7, R^8, R^9, R^{10} or R^6, is exemplified by the same hydrocarbon groups as those exemplifying the "hydrocarbon group that may be substituted" shown by R^1, R^2 or R^3 above.

The "hydrocarbon group that may be substituted" shown by R^7, R^8, R^9, R^{10} or R^6, may have 1 to 3 optionally chosen substituents at any possible positions, these substituents being exemplified by the same substituents as those defined for the "hydrocarbon group that may be substituted" shown by R^1, R^2 or R^3 above.

The "heterocyclic group that may be substituted"

shown by R^7, R^8, R^9, R^{10} or R^6, is exemplified by the same heterocyclic groups as those for the "het rocyclic group that may be substituted" shown by R^1, R^2 or R^3 above.

The "heterocyclic group that may be substituted" shown by R^7, R^8, R^9, R^{10} or R^6, may have 1 to 3 optionally chosen substituents at any possible positions, these substituents being exemplified by the same substituents as those defined for the "heterocyclic group that may be substituted" shown by R^1, R^2 or R^3 above.

The "acyl group" shown by R^4 is exemplified by aliphatic acyl groups such as alkanoyl groups (e.g., lower alkylcarbonyl groups such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl and hexanoyl), alkenoyl groups (e.g., lower alkenylcarbonyl groups such as acryloyl, methacryloyl, crotonoyl and isocrotonoyl), cycloalkanecarbonyl groups (e.g., cycloalkylcarbonyl groups such as cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl and cyclohexanecarbonyl), cycloalkenylcarbonyl groups (e.g., cyclopropenylcarbonyl, cyclobutenylcarbonyl, cyclopentenylcarbonyl, cyclohexenylcarbonyl) and alkanesulfonyl groups (e.g., lower alkylsulfonyl groups such as mesyl, ethanesulfonyl and propanesulfonyl); aromatic acyl groups such as aroyl groups (e.g., arylcarbonyl groups such as benzoyl, p-toluoyl, 1-naphthoyl and 2-naphthoyl), arylalkanoyl groups (e.g., alkylcarbonyl groups substituted with aryl groups, such as phenylacetyl, phenylpropionyl, hydroatropoyl and phenylbutyryl), arylalkenoyl groups (e.g., alkenylcarbonyl groups substituted with aryl groups, such as cinnamoyl and atropoyl) and arylsulfonyl groups (e.g., benzen sulfonyl group, p-toluenesulfonyl group); and aromatic acyl groups such as aromatic heterocyclic

carbonyl groups (e.g., furoyl, thenoyl, nicotinoyl, isonicotinoyl, pyrrolcarbonyl, oxazolcarbonyl, imidazolcarbonyl and pyrazolcarbonyl), aromatic heterocyclic alkanoyl groups (e.g., alkylcarbonyl groups substituted with aromatic heterocyclic groups, such as thienylacetyl, thienylpropanoyl, furylacetyl, thiazolylacetyl, 1,2,4-thiadiazolylacetyl and pyridylacetyl).

Of the above-mentioned acyl groups for R^4, those represented by the formula $-COR^9$ or $-SO_2R^6$ are preferable.

The groups represented by the formula $-COR^9$ are preferably represented by the formula $-COR^{9'}$ ($R^{9'}$ represents a hydrogen atom or an alkyl, alkenyl, aromatic hydrocarbon or aromatic heterocyclic group that may be substituted).

The "alkyl that may be substituted" shown by $R^{9'}$", is exemplified by lower (C_{1-6}) alkyls (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl).

The "alkenyl that may be substituted" shown by $R^{9'}$", is exemplified by lower (C_{2-6}) alkenyls (e.g., ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl).

The "alkyl that may be substituted" and "alkenyl that may be substituted" shown by $R^{9'}$, may each have 1 or 2 optionally chosen substituents at any possible positions, these substituents including aryl groups that may be substituted (preferably phenyl, 1-naphthyl, 2-naphthyl).

Such aryls may each have 1 or 2 optionally chosen substituents at any possible positions, these substituents including alkyl groups that may be

substituted (e.g., C_{1-3} alkyls such as methyl, ethyl and propyl). Such alkyl groups may each hav 1 or 2 optionally chosen substituents at any possible positions, these substituents including phosphono groups that may be substituted (e.g., dimethoxyphosphoryl, diethoxyphosphoryl).

The "aromatic hydrocarbon group that may be substituted" shown by $R^{9'}$, preferably includes phenyl, tolyl, xylyl, biphenyl, 1- or 2-naphthyl, 1-, 2- or 9-anthryl, 1-, 2-, 3-, 4- or 9-phenanthryl, 1-, 2-, 4-, 5- or 6-azulenyl and acenaphthylenyl, and, among them, phenyl, 1-naphthyl and 2-naphthyl, for example, are preferable.

The "aromatic hydrocarbon group that may be substituted" shown by $R^{9'}$, may have an optionally chosen substituent at any possible position, this substituent being exemplified by alkyls having 1 to 3 carbon atoms (e.g., methyl, ethyl, propyl) and halogens.

The "aromatic heterocyclic group that may be substituted" shown by $R^{9'}$, is preferably furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl, or the like.

The "aromatic heterocyclic group that may be substituted" shown by $R^{9'}$, may have an optionally chosen substituent at any possible position, this substituent being exemplified by alkyls having 1 to 3 carbon atoms (e.g., methyl, ethyl, propyl) and halogens.

As the group of the formula $-COR^{9'}$, mention is made of, for example, groups represented by the formula $-COR^{9''}$ [$R^{9''}$ stands for H, C_{1-10} alkyl, C_{2-10} alkenyl or an aromatic group], more specifically, formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl,

cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl or benzoyl, nicotinoyl.

The group represented by the formula $-SO_2R^6$ is preferably represented by the formula $-SO_2R^{6'}$ ($R^{6'}$ represents an aryl group that may be substituted).

The "aryl group that may be substituted" shown by $R^{6'}$, is exemplified by phenyl, 1-naphthyl and 2-naphthyl. Said aryl group may have 1 or 2 optionally chosen substituents at any possible positions, these substituents including alkyl groups that may be substituted (e.g., C_{1-3} alkyls such as methyl, ethyl and propyl). such alkyl groups may each have 1 or 2 optionally chosen substituents at any possible positions, these substituents including phosphono groups that may be substituted for (e.g., dimethoxyphosphoryl, diethoxyhosphoryl).

As optionally esterified carboxyl groups shown by R^4, mention is made of, for example, groups represented by the general formula $-COOR^5$ [R^5 stands for C_{1-6} alkyl, C_{2-6} alkenyl or C_{6-10} aralkyl], more specifically, groups formed by combination of carboxyl group with a C_{1-6} alkyl group, namely, for example, C_{1-6} alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec.-butoxycarbonyl, tert.-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl), groups formed by combination of carboxyl group with a C_{2-6} alkenyl group, namely, for example, C_{2-6} alkenyloxycarbonyl (e.g. allyloxycarbonyl, crotyloxycarbonyl, 2-pentenyloxycarbonyl and 3-hexenyloxycarbonyl), and groups formed by combination of carboxyl group with a C_{6-10} aralkyl group, namely, for example, C_{6-10} aralkyloxycarbonyl (e.g. benzyloxycarbonyl and phenethyloxycarbonyl).

As the "optionally substituted straight-chain or branched divalent hydrocarbon groups having a chain

length of 1 to 4 atoms as the linear moiety" shown by X, the carbon chain of a chain length of 1 to 4 atoms, that may be substituted, may be any one, as long as it is a divalent chain whose linear moiety consists of 1 to 4 atoms. The divalent chain constituting the linear moiety is exemplified by alkylene chains represented by $-(CH_2)_{k1}-$ (k_1 represents an integer of 1 to 4), alkenylene chains represented by $-(CH_2)_{k2}-(CH=CH)-(CH_2)_{k3}-$ (k_2 and k_3, whether identical or not, represent 0, 1 or 2, the sum of k_2 and k_3 being not more than 4) and C_{2-6} alkinylene chains. Said substituent may be any one, as long as it is capable of binding to the divalent chain constituting the linear moiety. such substituents include lower alkyls having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl), lower (C_{3-7}) cycloalkyls (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl), phosphono groups that may be esterified, carboxyl groups that may be esterified and hydroxyl group, with preference given to lower alkyls having 1 to 6 carbon atoms, more preferably C_{1-3} alkyls. Said ester of the carboxyl group that may be esterified is exemplified by those resulting from binding of a carboxyl group and an alkyl group having 1 to 6 carbon atoms, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert.-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl.

Examples of optionally substituted straight-chain or branched divalent hydrocarbon groups having a chain length of 1 to 4 atoms as the linear moiety shown by X include C_{1-4} alkylene groups (e.g. methylene, ethylene, propylene, trimethylene, tetramethylene, ethylmethylene, propylmethylene, isopropylmethylene and ethylethylen), C_{2-6} alkenylene groups (e.g. vinyl ne,

propenylene, 1- or 2-butenylene, butadielenylene, 1-methylvinylene, 1-ethylvinylene, 1-propylvinylene, 1-isopropylvinylene, butylvinylene, isobutylvinylene, 1-methylpropanylene, 2-methylpropanylene, 1-ethylpropanylene, 2-propylpropanylene and 1-isopropylpropanylene), C_{2-6} alkynylene groups (e.g. ethynylene, 1- or 2-propynylene, 1- or 2-butynylene, methylethynylene, propylethynylene, isobutylethynylene, tert.-butylethynylene, 1-methyl-1-propynylene, 2-methyl-1-propynylene, 3-methyl-2-propynylene, 1-ethyl-2-propynylene, 1-propyl-2-propynylene and 1-isopropyl-2-propynylene). These groups may optionally have 1 to 3 substituents at any possible position. As the substituents, mention is made of similar ones to those exemplified as substituents in the optionally substituted hydrocarbon groups shown by R^1, R^2 and R^3. Specific examples of the substituted straight-chain or branched divalent hydrocarbon groups include benzylmethylene, benzylethylene, 1-benzylpropylene, 2-benzylpropylene, 3-indolylmethylmethylene, 3-indolylmethylethylene, 1-(3-indolylmethyl)propylene, 2-(3-indolylmethyl)propylene, parahydroxylbenzylmethylene, 4-imidazolylmethylmethylene, methylthioethylmethylene and 1-(methylthioethyl)propylene.

With respect to the combination of m and n in the formula (Ia-Q), it is that (i) m is 1 and n is 1, (ii) m is 1 and n = 0 and (iii) m is 0 and n = 0, preferably (i) and (ii), more preferably (ii).

In the formula (Ia'-Q'), n is preferably 0.

The compound of the present invention is exemplified by the following:

·N-valproyl-(L)-valine (1S)-3-formyl-1-(3-indolylm thyl)-2-propenylamide

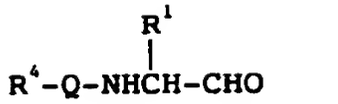
·N-benzyloxycarbonyl-(L)-alanyl-(L)-alanine (1S)-3-formyl-1-benzyl-2-propenylamide.

·N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-(3-indolylmethyl)propylamide
·N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-benzylpropylamide

In the present invention, the salts of the compounds of general formulas (Ia) and (I) are preferably physiologically acceptable salts, exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids and salts with organic acids, and salts with basic or acidic amino acids. Preferable salts with inorganic bases include alkali metal salts such as sodium salts and potassium salt; alkaline earth metal salts such as calcium salt and magnesium salt; and aluminum salt. Preferable salts with organic bases include ammonium salt, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylene diamine. Preferable salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid. Preferable salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzene sulfonic acid and p-toluenesulfonic acid. Preferable salts with basic amino acids include salts with arginine, lysine and ornithine. Preferable salts with acidic amino acids include salts with aspartic acid and glutamic acid.

Production methods for the compound (I) of this invention are hereinafter described in detail.

The compound (Ia) can be produced by allowing a compound represented by the gen ral formula (IIa)

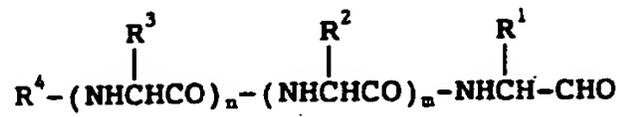


(IIa)

wherein Q stands for a direct bond or one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; and R^4 stands for an optionally esterified carboxyl group or an acyl group, or a salt thereof, to react, as described below in detail, with an acetaldehdye derivative, followed by, upon necessity, subjecting the reaction mixture to reduction.

And, the compound of the formula (I):

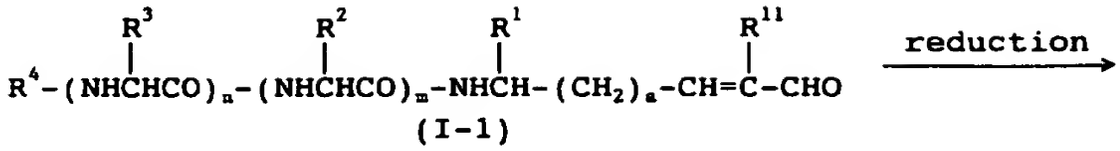
wherein R^1, R^2 or R^3 independently stand for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety; and m and n independently denote 0 or 1,
can be produced by allowing a compound represented by the formula (II)



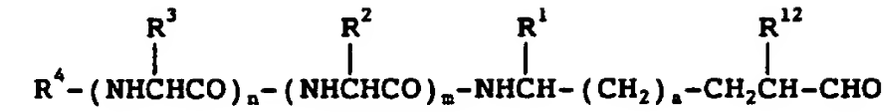
(II)

wherein all symbols are of the same meaning, or a salt thereof, to react, as described below in detail, with an acetaldehyde derivative, followed by, upon necessity, subjecting the reaction mixture to reduction.

Method A



(I-1)



(I-2)

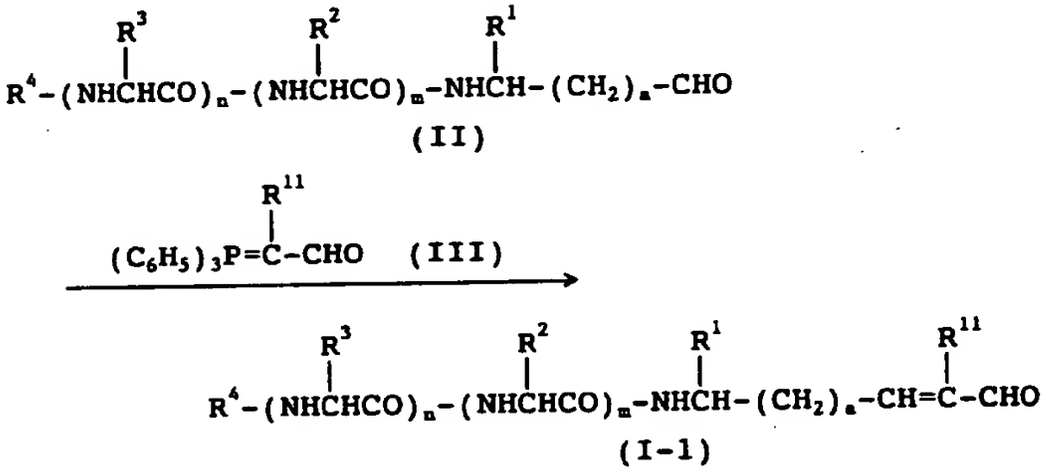
wherein the symbol a denotes 0, 1 or 2; R^{11} and R^{12} stand for H or an optionally substituted hydrocarbon group; and other symbols are of the same meaning as defined above.

Examples of the optionally substituted hydrocarbon group shown by R^{11} include C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl and isobutyl and C_{2-4} lower alkenyl groups such as vinyl, propenyl and butenyl, and these groups may optionally have 1 to 3 substituents on any possible position. As such substituents, mention is made of ones similar to those exemplified as substituents in the optionally substituted hydrocarbon groups shown by R^1, R^2 and R^3. As the optionally substituted hydrocarbon groups shown by R^{12}, mention is made of, among the ones exemplified as R^{11}, saturated ones.

The compound (I-2) is produced by subjecting the compound (I-1) to reduction. This reduction is conducted, in accordance with a conventional method, in a solvent in the presence of a catalyst under hydrogen atmosphere of 1 to 150 atm. Examples of the solvent include alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; halogenated hydrocarbons such as

chloroform, dichloromethane and 1,1,2,2-tetrachloroethane; ethyl acetate, acetic acid or suitable mixture of these solvents. As the catalyst, use is made of a metal such as a nickel compound or a transition metal catalyst such as palladium, platinum and rhodium, for conducting the reaction more advantageously. The reaction temperature ranges from 0 to 100°C, preferably from 10 to 80°C. The reaction time ranges from 0.5 to 50 hours.

Method B



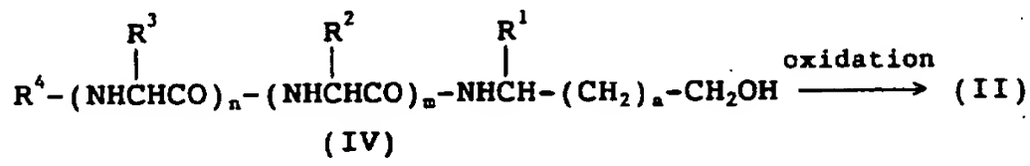
wherein symbols are of the same meaning as defined above.

In this method, an aldehyde derivative (II) is allowed to react with a (triphenylphosphoranyliden) acetaldehyde derivative (III) to give an unsaturated aldehyde derivative (I-1). The reaction of (II) with (III) is conducted, in accordance with a conventional method, in an adequate solvent. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; alcohols such as methanol, ethanol and propanol; N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and suitable mixture of these solvents. The amount of the comp und

(III) to be employed ranges from 1 to 5 molar quivalents, preferably 1 to 3 molar equivalents, relative to the compound (II). This reaction is conducted at temperatures usually ranging from -50°C to 150°C, preferably from about -10°C to 100°C. The reaction time ranges from 0.5 to 30 hours.

The method of producing the compound (II) is hereinafter described in detail.

Method C



(IV)

wherein each symbol is of the same meaning as defined above.

This oxidation reaction is conducted in accordance with a per se known oxidation reaction. For example, oxidation using chromic acid, such as Jones oxidation using chromium oxide-sulfuric acid-pyridine, Collins oxidation using chromium oxide-pyridine complex, oxidation using pyridinium chlorochromate (PCC) and oxidation using pyridinium dichromate (PDC); oxidation using activated DMSO and oxidation using oxoammonium salt.

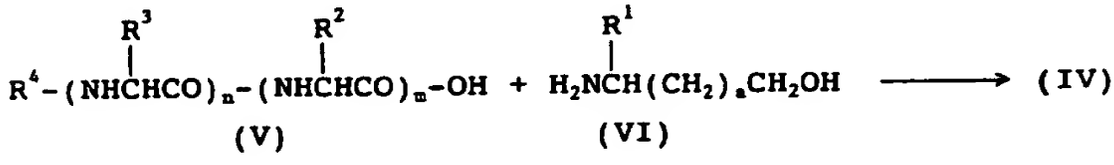
In the case of optically active compounds, oxidation is conducted advantageously by activated dimethyl sulfoxide (DMSO) oxidation. The activated DMSO oxidation is conducted in a solvent in the co-presence of DMSO and an electrophilic reagent. Examples of the solvent include ethers such as ethyl ether, isopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as N,N-dimethylformamide (DMF), chloroform and dichloromethane; pyridine and dimethyl sulfoxide. These solvents are employed by adequately selected

depending on the kinds of an electrophilic reagent. Methods of activated DMSO oxidation include the dicyclohexylcarbodiimide (DCC) method, the acetic anhydride method, the phosphorus pentoxide method, the chlorine method, the sulfur trioxide-pyridine method, the keteneimine-enamine method and the mercury (II) acetate method, named according to the electrophilic reagent used. This oxidation is advantageously carried out by the sulfur trioxide-pyridine method, in which oxidation is achieved using a sulfur trioxide-pyridine complex as a DMSO activator reagent in the presence of triethylamine. The reaction can also be carried out using dimethyl sulfoxide as a solvent. The amount of triethylamine and sulfur trioxide-pyridine complex to be employed ranges from 1 to 10 molar equivalents, preferably from 2 to 5 molar equivalents, relative to the compound (IV). The reaction temperature ranges from -70 to 80°C, preferably from -20°C to 40°C. The reaction time ranges from 0.5 to 10 hours.

The aldehyde derivative (II) thus obtained can be isolated and purified by known means of separation and purification, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

Among the starting compounds in this invention, the compounds (IV), can be produced by, for example, the following method.

Method D



wherein each symbol is of the same m aning as defined above.

In this method, the compound (V) or its reactive

derivative at the carboxyl group or a salt thereof is allowed to react with the compound (VI) or its reactive derivative at the amino group or a salt thereof to yield the compound (IV). Preferable derivatives of the compound (VI) at the amino group thereof include Schiff's base type imino or enamine form tautomeric isomers resulting from reaction of the compound (VI) with a carbonyl compound such as aldehyde or ketone; silyl derivatives resulting from reaction of the compound (VI) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl) acetamide or bis(trimethylsilyl)urea; and derivatives resulting from reaction of the compound (VI) with phosphorus trichloride or phosgene. As preferable salts of the compound (IV) and its reactive derivatives, reference is made to acid adduct salts exemplified in connection with the compound (I).

Preferable reactive derivatives of the compound (V) at the carboxyl group thereof include acid halides, acid anhydrides, activated amides and activated esters. Preferable examples of the reactive derivatives include acid chlorides; acid azides; mixed acid anhydrides such as those with a substituted phosphoric acid such as dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid or halogenated phosphoric acid, or with dialkylphosphorous acid, sulfurous acid, thiosulfuric acid or sulfuric acid, or with a sulfonic acid such as methanesulfonic acid, or with an aliphatic carboxylic acid such as acetic acid, propionic acid, butyric acid, isobutyropivalic acid, pentanoic acid, isopentanoic acid or trichloroacetic acid or with an aromatic carboxylic acid such as benzoic acid; symmetric acid anhydrides; activated amides with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; activat d esters such as cyanomethyl ester,

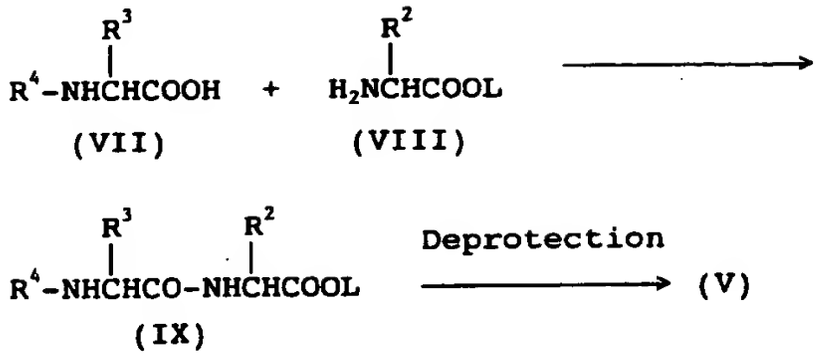
methoxymethyl ester, dimethyliminomethyl ester, vinyl ester, propargyl ester, p-nitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenyl ester, p-cresylthio ester, carboxymethylthio ester, pyranyl ester, pyridyl ester, piperidyl ester and 8-quinolylthio ester, and esters with N-hydroxy compounds such as N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide and 1-hydroxy-1H-benzotriazole. These reactive derivatives can be optionally chosen depending on the kinds of compound (V) then employed. Preferable salts of reactive derivatives of compound (V) include salts with bases, exemplified by alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as calcium salt and magnesium salt, ammonium salt, and organic base salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt and N,N-dibenzylethylenediamine salt. This reaction is normally carried out in a conventional solvent such as water, alcohol such as methanol and ethanol, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide or pyridine, but can be carried out in any other organic solvent, so long as it does not interfere with the reaction. These conventional solvents may be used as a mixture with water.

When the compound (V) is used in the form of free acid or a salt thereof, this reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimid ; N-cyclohexyloxy-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-

diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride; diphenylphosphorylazide; thionyl chloride, oxalyl chloride; a lower alkyl haloformate such as ethyl chloroformate or isopropyl chloroformate; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt, 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; N-hydroxybenzotriazole; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; or what is called Vilsmeier's reagent as prepared by reaction of N,N'-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate or phosphorus oxychloride. This reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal hydrogen carbonate tri(lower)alkylamine, pyridine, N-(lower)-alkylmorpholine or N,N-di(lower)alkylbenzylamine. Although the reaction temperature is not subject to limitation, this reaction is usually carried out under cooling to warming conditions.

The compound (V), which is a starting compound in Method D, is produced in accordance with the following Method E to Method L.

Method E



wherein L stands for a carboxy-protecting group, and other symbols are of the same meaning as defined above.

The carboxy-protecting group shown by L is exemplified by protecting groups in common use in the field of peptide synthesis, such as ester derivatives.

In this method, the compound (VII) or its reactive derivative at the carboxyl group or a salt thereof is allowed to react with the compound (VIII) or its reactive derivative at the amino group or a salt thereof to yield the compound (IX), which is then subjected to a deprotection reaction to remove the carboxy-protecting group to yield the compound (V). The reaction of the compound (VII) or its reactive derivative at the carboxyl group or a salt thereof with the compound (VIII) or its reactive derivative at the amino group or a salt thereof is carried out in substantially the same manner as in Method D.

The deprotecting reaction of the compound (IX) to remove its carboxy-protecting group can be conducted by any common method of removing a carboxyl-protecting group, such as deprotection by hydrolysis, reduction or a Lewis acid. The hydrolysis is carried out preferably in the presence of a base or an acid. Preferable bases include inorganic bases such as alkali metal hydroxides (e.g. sodium hydroxide and potassium hydroxide), alkaline earth metal hydroxides (e.g. magnesium

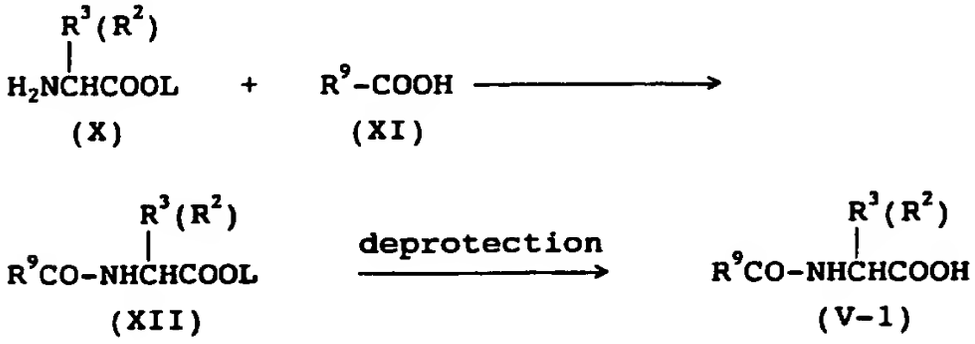
hydroxide and calcium hydroxide), alkali metal carbonates (e.g. sodium carbonate and potassium carbonate), alkaline earth metal carbonates (e.g. magnesium carbonate and calcium carbonate), alkali metal hydrogencarbonates (e.g. sodium hydrogencarbonate and potassium hydrogencarbonate), alkali metal acetates (e.g. sodium acetate and potassium acetate), alkaline earth metal phosphates (e.g. magnesium phosphate and calcium phosphate) and alkali metal hydrogenphosphates (e.g. disodium hydrogenphosphate and dipotassium hydrogenphosphate), and organic bases such as trialkylamine (e.g. trimethylamine and triethylamine), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]non-5-ene and 1,8-diazabicyclo[5.4.0]-7-undecene. Hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixture of them. Preferable acids include organic acids (e.g. formic acid, hydrobromic acid and sulfuric acid).

This hydrolysis is usually carried out in an organic solvent, water or a mixture of them. Reaction temperature, not subject to limitation, is chosen appropriately depending on the kind of carboxy-protecting groups and the method of deptotection then employed. Deprotection using a Lewis acid is carried out by allowing the compound (IX) or a salt thereof to react with a Lewis acid such as a boron trihalide (e.g. boron trichloride and boron trifluoride), a titanium tetrahalide (e.g. titanium tetrachloride and titanium tetrabromide), an aluminum trihalide (e.g. aluminum chloride and aluminum bromide), trihaloacetic acid (e.g. trichloroacetic acid and trifluoroacetic acid). This deprotecting r action is preferably carried out in the pr sence of a cation capturing agent (e.g. anisole and phenol) and usually carried out in a solvent which

does not interfere with the reaction, such as a nitroalkane (e.g. nitromethane and nitroethan), an alkylene halide (e.g. methylene chloride and ethylene chloride), diethyl ether and carbon disulfide. These solvents may be used as a suitable mixture of them.

Deprotection by reduction is preferably applied to removing the protecting groups such as esters of haloalkyls (e.g. 2-iodoethyl and 2,2,2-trichloroethyl) and esters of aralkyl (e.g. benzyl). Method of reduction for this deprotection reaction include reduction with a combination of a metal (e.g. zinc and zinc amalgam) or a chromium compound salt (e.g.chromous chloride and chromous acetate) and an organic or inorganic acid (e.g. acetic acid, propionic acid and hydrochloric acid); and a conventional catalytic reduction in the presence of a common metal catalyst (e.g. palladium-carbon, Raney nickel). Although the reaction temperature for this reaction is not subject to limitation, the reaction is conducted usually under cooling, at room temperature or under warming.

Method F

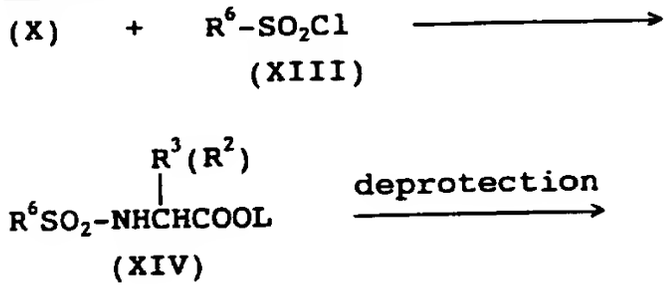


wherein each symbol is of the same meaning as defined above.

In this method, the compound (XI) or its reactive derivative at the carboxyl group or a salt thereof is allowed to react with the compound (X) or its reactive derivative at the amino group or a salt thereof to yield the compound (XII), which is then subject d to

deprotection reaction to r move its carboxy-protecting group to yield the compound (V-1). This method is carried out in substantially the same manner as in Method E.

Method G



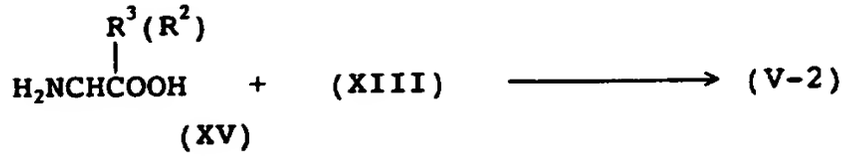
wherein each symbol is of the same meaning as defined above.

In this method, the compound (XIII) or a salt thereof is allowed to react with the compound (X) or a salt thereof to yield the compound (XIV), which is then subjected to a deprotecting reaction to remove its carboxyl-protecting group to give the compound (V-2). The reaction of (X) with (XIII) is carried out in an appropriate solvent. This solvent is exemplified by aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as dioxane, tetrahydrofuran and dimethoxyethane, alcohols such as methanol, ethanol and propanol, ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone, 2-butanone and a suitable mixture of these solvents.

The reaction of (X) with (XIII) is carried out in the presence of an appropriate base exemplified by alkali metal salts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate and sodium hydorgencarbonate, amines such as pyridine, triethylamine and N,N-dimethylaniline, sodium hydride and potassium hydride. The amount of these bases to be employed ranges preferably from about 1 to 5 molar

equivalents, relative to the compound (X). This reaction is carried out at temperatures usually ranging from -20 to 150°C, preferably from about -10 to 100°C. The compound (XIV) thus obtained is subject to a deprotecting reaction to yield the compound (V-2). This deprotection is carried out in substantially the same manner as in Method F.

Method H



wherein each symbol is of the same meaning as defined above.

In this method, the compound (XV) or a salt thereof is allowed to react with the compound (XIII) or a salt thereof to yield the compound (V-2). This sulfonylation is usually carried out under what is called Schotten Baumann's conditions, in which the amino acid derivative (XV), prepared as an aqueous solution of sodium salt thereof, is allowed to react with the compound (XIII), followed by subjecting the reaction mixture to acidification.

Method I

wherein each symbol is of the same meaning as defined above.

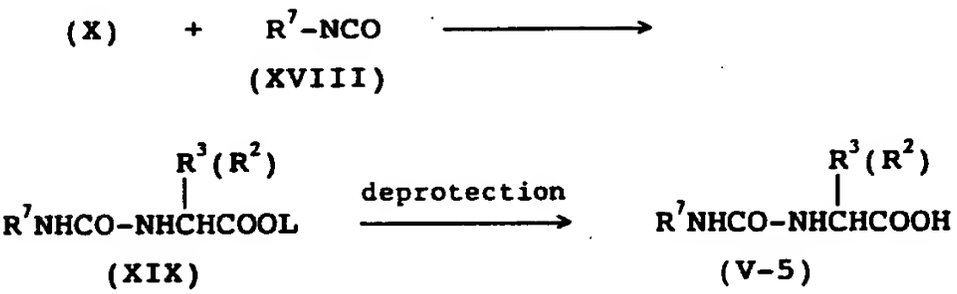
In this method, the compound (XV) or a salt thereof is allowed to react with the compound (XVI) or a salt thereof to yield the compound (V-3). This acylation is carried out substantially the same manner as in Method H.

Method J

wherein each symbol is of the same meaning as defined above.

In this method, the compound (XV) or a salt thereof is allowed to react with the compound (XVII) or a salt thereof to yield the compound (V-4). This method is carried out in substantially the same manner as in Method I.

Method K

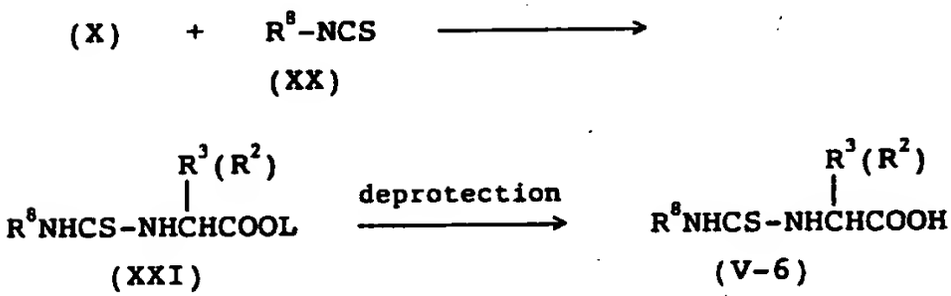


wherein each symbol is of the same meaning as defined above.

In this method, the compound (X) or a salt thereof is allowed to react with the compound (XVIII) to yield the compound (XIX), which is then subjected to a deprotecting reaction to remove its carboxy-protecting group to give the compound (V-5). The reaction of the compound (X) or a salt thereof with the compound (XVIII) is carried out in an appropriate solvent. This solvent is exemplified by aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as dioxane, tetrahydrofuran and dimethoxyethane, ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone, 2-butanon and a

suitable mixtur of these solvents. The amount of the compound (XVIII) to be employed ranges preferably from about 1 to 5 molar equivalents, relative to the compound (X). The reaction is conducted usually at temperatures ranging from -20 to 150°C, preferably from about -10 to 100°C. The compound (XIX) thus obtained is subjected to a deprotecting reaction to yield the compound (V-5). This deprotection is carried out in substantially the same manner as in Method E.

Method L

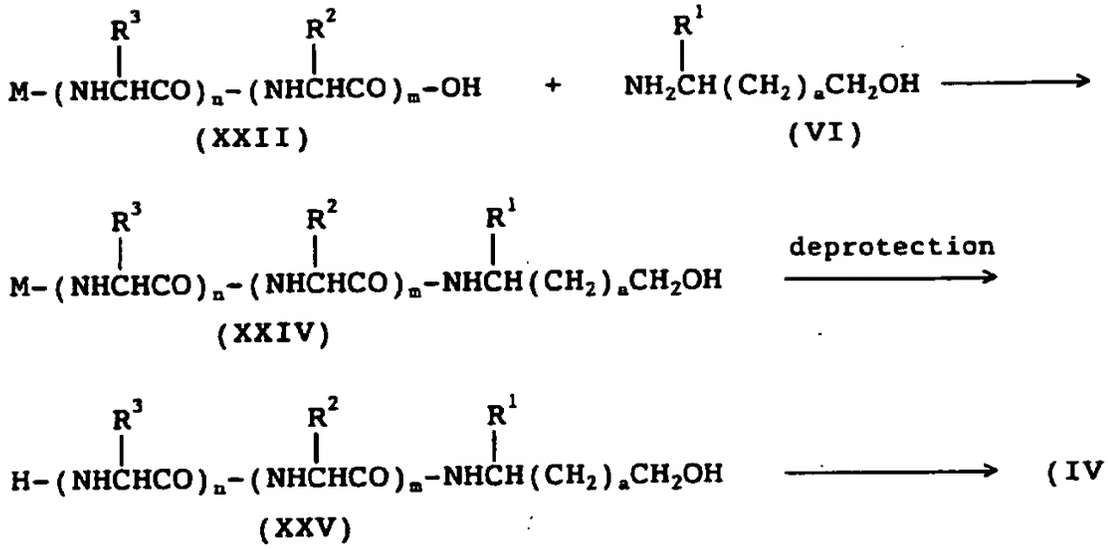


wherein each symbol is of the same meaning as defined above.

In this method, the compound (X) or a salt thereof is allowed to react with the compound (XX) to yield the compound (XXI), which is then subjected to a deprotecting reaction to remove the carboxy-protecting group to give the compound (V-6). This reaction is carried out in substantially the same manner as in Method K.

The starting compound (IV) in Method C can also be produced by the following method.

Method M



wherein M stands for an amino-protecting group, and other symbols are of the same meaning as defined above.

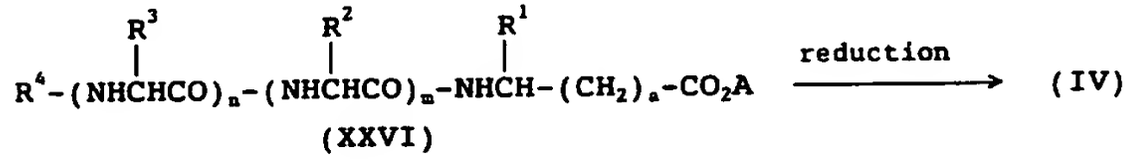
The amino-protecting group shown by M is exemplified by protecting groups in common use in the field of peptide synthesis, such as oxycarbonyl derivatives, with preference given to benzyloxycarbonyl.

In this method, the compound (XXII) or its reactive derivative at the carboxyl group or a salt thereof is allowed to react with the compound (VI) or its reactive derivative at the amino group or a salt thereof to yield the compound (XXIV), which is then subjected to a deprotecting reaction to remove the amino-protecting group to give the compound (XXV). The reaction of the compound (XXII) or its derivative reactive at the carboxyl group or a salt thereof with the compound (VI) or its derivative reactive at the amino group or a salt thereof is carried out in substantially the same manner as in Method D. In the amino-protecting group removing reaction of the compound (XXIV), the amino-protecting group can be removed by any common method employed for the reaction to remove the amino-protecting group. For example, the benzyloxycarbonyl group is removed by catalytic

reduction in the presence of a conventional metal catalyst (e.g. palladium-carbon and Raney nickel). Reaction temperature is not subject to limitation, and the reaction is carried out usually under cooling, at room temperature or under warming. Then, the compound (XXV) is acylated in substantially the same manner as in the reaction of the compound (X) with the compound (XI) in Method F or the reaction of the compound (XV) with the compound (XVI) in Method F, sulfonylated in substantially the same manner as in the reaction of the compound (X) with the compound (XIII) in Method G, oxycarbonylated in substantially the same manner as in the reaction of the compound (XV) with the compound (XVII) in Method J, carbamoylated in substantially the same manner as in the reaction of the compound (X) with the compound (XVIII) in Method K, and then thiocarbamoylated in substantially the same manner as in the reaction of the compound (X) with the compound (XX) in Method L, to yield the compound (IV).

A portion of the starting compound (IV) of this invention can be produced by, for example, the following method.

Method N



(XXVI)

wherein A stands for a lower alkyl group, and other symbols are of the same meaning as defined above.

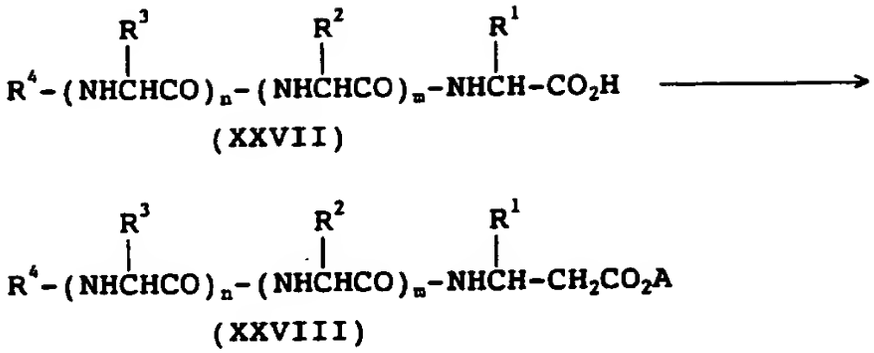
Examples of the lower alkyl group shown by A include C_{1-4} ones such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl and sec.-butyl.

This reduction can be carried out by a per se known method, for example, reduction by using metal hydride, reduction by using a metal hydride complex

compound and reduction by using diborane or a substituted borane. In other words, this reaction is carried out by processing the compound (XXVI) with a reducing agent. Examples of the reducing agent include metal hydride complex compounds such as alkali metal borohydrides (e.g. sodium borohydride and lithium borohydride) and lithium aluminum hydride and diborane and so on, and the reduction is advantageously carried out by the use of lithium borohydride. This reaction is carried out in an organic solvent which does not interfere with the reaction. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene, halogenated hydrocarbons such as chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, ethers such as diethyl ether, tetrahydrofuran and dioxane, alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol, amides such as N,N-dimethylformamide or a suitable mixture of these solvents. From among these solvents, a suitable one is chosen depending on the kind of the reducing agent then employed. The reaction temperature ranges from -20°C to 150°C, especially the range from 0 to 100°C is preferable. The reaction time ranges from about 1 to 24 hours.

The starting compound (XXVI) in Method N can be produced by, for example, repeating the following chain-elongation reaction.

Method Q



(XXVII)

(XXVIII)

wherein each symbol is of the same meaning as defined above.

This chain-elongation reaction is carried out by a per se known method. More specifically, in this method, a reactive derivative of the compound (XXVII) at the carboxyl group is allowed to react with diazomethane to yield a diazomethylketone derivative, which is then subjected to Wolff Rearrangement in the presence of silver oxide to give the compound (XXVIII). As the reactive derivative of the compound (XXVII) at the carboxyl group, mention is made of, for example, reactive derivatives described in Method D. The reaction of the reactive derivative of the compound (XXVII) at the carboxyl group with diazomethane is carried out in an inert solvent. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene, halogenated hydrocarbons such as chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, ethers such as diethyl ether, tetrahydrofuran and dioxane, amides such as N,N-dimethylformamide or a suitable mixture of these solvents. The subsequent Wolff Rearrangement reaction of the diazomethylketone is carried out in an alcoholic solvent, pr ferably exemplified by methanol, thanol, propanol, isopropanol, butanol, s c.-butanol and 2-

methoxyethanol.

The compound represented by the formula (Ia) described above can be produced by a method analogous to that of producing the compound represented by the formula (I-1) or (I-2) described above, in which at least one of m and n denotes 1.

And, the compound represented by the formula (IIa) described above can be produced by a method analogous to that of producing the compound represented by the formula (II) described above, in which at least one of m and n denotes 1.

In the present invention, the compound of the formula (Ia) or (I) can be administered orally or non-orally, as formulated by admixing an effective dose with a physiologically acceptable carrier in the form of solid preparations such as tablets, capsules, granules or powdery compositions; or liquid preparations such as syrup and injectable preparations.

Pharmaceutically acceptable carriers are various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders and disintegrating agents for solid preparations, and solvents, solubilizers, suspending agents, isotonizing agents, buffers and soothing agents for liquid preparations. Other pharmaceutical additives such as preservatives, antioxidants, coloring agents and sweetening agents may be used upon necessity.

Preferable excipients include lactose, sucrose, D-mannitol, starch, crystalline cellulose and light silicic acid anhydride.

Preferable lubricants include magnesium stearate, calcium stearate, talc and colloidal silica.

Preferable binders include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and polyvinylpyrrolidone.

Preferable disintegrating agents include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, cross carmellose sodium and carboxymethyl starch sodium.

Preferable solvents include water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil.

Preferable solubilizers include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, tris-aminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Preferable suspending agents include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol, and hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxyproplyl cellulose.

Preferable isotonizing agents include sodium chloride, glycerol and D-mannitol.

Preferable buffers include buffer solutions of phosphates, acetates, carbonates and citrates.

Preferable soothing agents include benzyl alcohol.

Preferable preservatives include p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Preferable antioxidants include sulfites and ascorbic acid.

As the cysteine protease, which is the subject of this invention, mention is made of protease having thiol group at the center of enzymic activity, which is specifically exemplified by cathepsin L, cathepsin B and carpaine.

The compounds of the formulae (Ia) and (I) possess a strong action of inhibiting cystein protease and can

be safely used with low toxicity. Therefore, the compounds of the formula (Ia) and (I) can be used for the prophylaxis or therapy of diseases (for example, osteoporosis, hypercalcemia, arthrosis such as rheumatoid arthritis, inflammatory, propagation of tumor cells, cancer metastasis, myodystrophy, muscular atrophy, Alzheimer's disease, various autoimmune diseases such as rhematoid arthritis, multiple sclerosis, myathemia gravis, insulin dependent diabetes mellitus (type I diabetes mellitus), inflammatory bowl diseases, systemic lupus erythematosus, glomerulonephritis, autoimmune hemolytic anemia, Hashimoto's disease, idiopathic ulcerative colitis, primary biliary cirrhosis, idiopathic thrombocytopenic purpura, sympathetic ophthalmia, permicious anemia, Sjögren's syndrome and Goodpasture's syndrome), in which cysteine protease participate, in mammals (e.g. mice, rats, rabbits, dogs, cats, bovines, swine and humans).

When using the compounds (Ia) and (I) or a salt thereof as a prophylactic/therapeutic agent of diseases, in which cysteine protease participate, the daily dose ranges from about 1 to 1000 mg, preferably from about 10 to 500 mg, depending on patient condition and weight and method of administration, for each adult (weighing 50 kg), in 1 to 3 portions per day, in the case of oral administration.

Best Mode for Carrying Out the Invention

The actions of the compounds (Ia) and (I) are hereinafter described by means of the following experimental examples.

Experimental Example 1

(Determination of human cathepsin L inhibitory activity)

A purified recombinant human cathepsin L was diluted with a diluent [0.1% Brij 35 (produced by Sigma

Chemical Co.)] to a concentration of 1 μg/ml. One μl of this enzyme dilution was mixed with 46 μl of the diluent, 2 μl of 0.1M DTT and 25 μl of an activator/buffer (340 mM sodium acetate, 60 mM acetic acid, 4mM disodium EDTA, pH 5.5). To this mixture were added a 1 μl of the sample diluted to 10^{-2}M with dimethyl sulfoxide (DMSO) and 25 μl of 20μM Z-Phe-Arg-NHMec (enzyme substrate solution), followed by incubation at 30°C. Then, 100 μl of a reaction stopper (100 mM sodium monochloroacetate, 30 mM sodium acetate, pH 4.3) was added. This reaction was conducted on a 96-well fluoroplate (manufactured by Labo Systems).

After the reaction was suspended, the fluorescence intensity of liberated aminomethylcoumarin was determined at a wavelength of 450 nm (excitation wavelength = 365 nm), using a fluorometer FCA (manufactured by Baxter Travenol). For a control, one μl of sample-free DMSO was added instead; fluorometric value obtained from this control reaction was taken as 100% activity. When the residual activity was not higher than 10%, the sample solution was further diluted and then assayed for residual activity in the same procedure as above to calculate the IC_{50} value. The results are given in Table 1.

Experimental Example 2

(Determination of rat cathepsin B inhibitory activity)

A rat cathepsin B was diluted with a diluent [0.1% Brij 35 (produced by Sigma Chemical Co.)] to a concentration of 30 μg/ml. One μl of this enzyme dilution was mixed with 46 μl of the diluent, 2 μl of 0.1M DTT and 25 μl of a buffer solution of 100 mM sodium phosphate (pH 6.5). To this mixture were added 1 μl of the sample diluted to 10^{-2}M with dimethyl sulfoxide (DMSO) and 25 μl of 20 μM Z-Phe-Arg-NHMec (enzyme substrate solution), followed by incubation at 37°C for 20 minutes. Then, 100 μl of a reaction

stopper (100 mM sodium monochloroacetate, 30 mM sodium acetat , pH 4.3) was added. This reaction was conducted on a 96-well fluoroplate (manufactured by Labo Systems).

After the reaction was stopped, the fluorescence intensity of liberated aminomethylcoumarin was determined at a wavelength of 450 nm (excitation wavelength = 365nm), using a fluorometer FCA (manufactured by Baxter Travenol). For a control, 1 µl of sample-free DMSO was added instead; the fluorometric value obtained from this control reaction was taken as 100% activity. When the residual activity was not higher than 10%, the sample solution was further diluted and then assayed for residual activity in the same procedure as above to obtain the IC_{50} value. The results are given in Table 1.

Table 1

Compound (No. of W. Ex.)	Enzyme Inhibitory Activity [IC_{50} (M)]	
	Cathepsin L	Cathepsin B
1	3.5×10^{-8}	2.4×10^{-6}
3	2.8×10^{-8}	6.6×10^{-7}
5	2.4×10^{-8}	2.3×10^{-7}
7	3.9×10^{-8}	9.2×10^{-7}
8	9.7×10^{-9}	9.7×10^{-7}
10	6.2×10^{-8}	1.8×10^{-6}
13	3.8×10^{-8}	2.3×10^{-7}
16	6.7×10^{-8}	3.6×10^{-6}
17	6.0×10^{-8}	9.8×10^{-7}
18	6.0×10^{-8}	1.8×10^{-6}

Experimental Example 3

(Bone resorption suppressing action)

Bone resorption inhibitory activity was measured

by the method of Raisz [Journal of Clinical Investigation, 44, 103-116(1985)]. Specifically, one Sprague-Dawley rat, at 18 days of gestation, was given 50 μCi of ^{45}Ca (calcium isotope, in $CaCl_2$ solution) by subcutaneous injection. On the following day, the animal was laparotomized and fetal rats were aseptically removed. Both forearm bones (radium and ulna) were cut out from the body of each fetus under an anatomical microscope, and connective tissue and cartilages were removed to the maximum possible extent, to prepare bone culture samples. Each bone fragment was cultured at 37°C for 24 hours in 0.6 ml of BGJb medium (Fitton-Jackson modification; GIBCO Laboratories, the United States) prepared by adding bovine serum albumin (final concentration 2 mg/ml), after which it was transferred to the same medium as above but containing each compound (final concentration 10 μM) and cultured for two more days. ^{45}Ca radioactivity in the medium and ^{45}Ca radioactivity in the bone were then measured, and the percent ratio of ^{45}Ca released from the bone to the medium was calculated using the following equation:

$$\text{Percent ratio of } ^{45}Ca \text{ released from bone to medium} = \frac{(^{45}Ca \text{ count in the medium})}{[(^{45}Ca \text{ count in the medium}) + (^{45}Ca \text{ count in the bone})]} \times 100$$

For control, bone fractions from fetuses of the same litter were cultured for two days in the absence of the test compound. The mean standard deviation for the values from five bone fragments in each group was calculated, and their percent ratios to the control were calculated. The results are given in Table 2.

Table 2

Compound (No. of W. Ex.)	Bone Resorption Inhibitory Activity [^{45}Ca Release Rate (Percent to control)]
1	83
5	75
7	83
8	51
11	75
14	73
16	73

The present invention is hereinafter described in detail by means of, but not limited to, the following Reference Examples and Working Examples. Incidentally, optical rotation was measured at 20 to 25°C. The room temperature ranges from about 15°C to about 25°C.

Reference Example 1

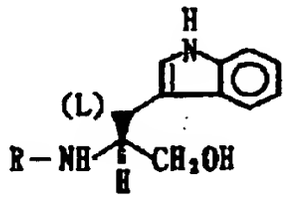
To a solution of benzyloxycarbonyl-(L)-tryptophanol (3.0 g) in methanol (40 ml) was added Pd-C (10%, 1.5g). Catalytic hydrogenation was conducted at room temperature under one atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give an oily product. To a solution of this oily product and t-butoxycarbonyl-(L)-phenylalanine (2.5 g) in N,N-dimethylformamide (40 ml) were added 1-hydroxybenzotriazole (HOBt) (1.58 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl)(1.98 g) at 0°C. The reaction mixture was stirred for 12 hours at room temperature, which was poured into ethyl acetate. The ethyl acetate layer was washed with a 10% aqueous solution of citric acid, a saturated aqueous solution of sodium hydrogencarbonate and brine, successively, followed by drying ($MgSO_4$). The solvent was th n distilled off to leave crystalline product, which was recrystallized from ethyl acetate-

hexane to give N-t-butoxycarbonyl-(L)-phenylalanyl-(L)-tryptophanol (2.4g, 60%), m.p.150-151°C.
$[\alpha]_D$=-20.2° (c=0.96,$CHCl_3$)(20°C).

Reference Examples 2 to 7

By substantially the same procedure as in Reference Example 1, compounds shown in [Table 3] were produced.

[Table 3]



No. of R. Ex.	R	m.p. (°C)	Recrystallization solvent	Optical Rotation $[\alpha]_D$ (c, solvent)
2	1-NapSO_2-Ile-	150-151	Dichloromethane-ether	-77.7° (c=0.57,$CHCl_3$)
3	$(C_3H_7)_2$CHCO-Val-	187-188	Ethylacetate-hexane	-35.8° (c=0.50,CH_3OH)
4	2-NapSO_2-Ile-	215-217	Ethylacetate	-4.5° (c=0.61,DMSO)
5	1-NapNHCO-Ile-	217-218	Ethylacetate-methanol	-5.6° (c=0.33,DMSO)
6	$PhCH_2OCO$-Leu-Leu-	154-156	Ethylacetate-hexane	-54.1° (c=0.73,CH_3OH)
7	$(PhCH_2)_2$CHCO-	120-122	Ethylacetate-hexane	-13.9° (c=0.62,$CHCl_3$)

Ile: (L)-isoleucine, Val: (L)-valine, Leu: (L)-leucine, 1-Nap: 1-naphthyl, 2-Nap: 2-naphthyl, Ph: phenyl, DMSO: dimethyl sulfoxide

Reference Example 8

By substantially the same procedure as in Reference Example 1, N-α-naphthalen sulfonyl-(L)-isoleucyl-(L)-alaninol was produced, which was recrystallized from ethyl ac tate-hexane.

m.p.178-179°C. $[\alpha]_D$=+54.3° (c=0.38,DMSO)(20°C).

Reference Example 9

By substantially the same procedure as in Reference Example 1, N-α-naphthalenesulfonyl-(L)-isoleucyl-(L)-phenylalaninol was produced, which was recrystallized from ethyl acetate-hexane. m.p.169-170°C. $[\alpha]_D$=-108.3° (c=0.65,$CHCl_3$)(20°C).

Reference Example 10

By substantially the same procedure as in Reference Example 1, N-benzyloxycarbonyl-(L)-alanyl-(L)-alanyl-(L)-phenylalaninol was produced, m.p.180-182°C. $[\alpha]_D$=-57.0°. (c=0.48,CH_3OH)(20°C).

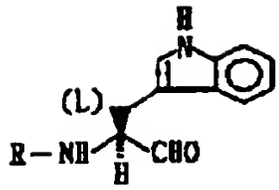
Reference Example 11

To a solution of N-t-butoxycarbonyl-(L)-phenylalanyl-(L)-tryptophanol (1.0 g) and triethylamine (0.69 g) in dimethyl sulfoxide (DMSO) (5 ml) was added dropwise a solution of a pyridine·SO_3 complex (1.1 g) in DMSO (5 ml). The mixture was stirred for one hour at room temperature, which was poured into ice-water, followed by subjecting to extraction with ethyl acetate. The ethyl acetate layer was washed with a 10% aqueous solution of citric acid, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous saline solution, successively, followed by drying ($MgSO_4$). The solvent was distilled off to leave crystalline product, which was recrystallized from ethyl acetate-hexane to give N-t-butoxycarbonyl-(L)-phenylalanyl-(L)-tryptophanal (0.50g, 50%), m.p.85-86°C. $[\alpha]_D$=+17.4°. (c=0.71,$CHCl_3$)(20°C).

Reference Examples 12 to 17

By substantially the same procedure as in Reference Example 11, compounds shown in [Table 4] were produced.

[Table 4]



No. of R. Ex.	R	m.p. (°C)	Recrystallization solvent	Optical Rotation $[\alpha]_D$ (c, solvent)
12	1-NapSO_2-Ile-	145-146	Ethylacetate-hexane	-48.9° (c 0.50,$CHCl_3$)
13	$(C_3H_7)_2$CHCO-Val-	149-150	Ethylacetate-hexane	-48.8° (c 0.50,CH_3OH)
14	2-NapSO_2-Ile-	172-173	Ethylacetate-hexane	+5.9° (c 0.43,$CHCl_3$)
15	1-NapNHCO-Ile-	192-193	Ethylacetate-hexane	+4.4° (c 0.40,DMSO)
16	$PhCH_2OCO$-Leu-Leu-	-[1)]	-	
17	$(PhCH_2)_2$CHCO-	142-144	Ethylacetate-IPE	+14.1° (c 0.57,$CHCl_3$)

Ile: (L)-isoleucine, Val: (L)-valine, Leu: (L)-leucine, 1-Nap: 1-naphthyl, 2-Nap: 2-naphthyl, Ph: phenyl, DMSO: dimethylsulfoxide, IPE: isopropyl ether

Note: oily product

^{1}H-NMR(δ ppm in $CDCl_3$): 0.7-1.0(12H,m), 1.3-1.8(6H,m), 3.26(2H,d,J=6.0Hz), 4.1-4.2(1H,m), 4.4-4.6(1H,m), 4.6-4.8(1H,m), 5.05(2H,ABq, J=3.6 & 11.6Hz), 5.29(1H,brd,J=6.6Hz), 6.55(1H,brd,J=8.0Hz), 6.9-7.4(5H,m), 7.32(5H,s), 7.55(1H,d,J=7.0Hz), 8.37(1H,brs), 9.58(1H,s).

Reference Example 18

By substantially the same procedure as in Reference Example 11, N-α-naphthalenesulfonyl-(L)-isoleucyl-(L)-alaninal was produced, which was recrystallized from ethyl ac tate-hexane.

m.p.150-151°C $[\alpha]_D$=+36.7° (c=0.45,DMSO)(20°C).

Reference Example 19

By substantially the same procedure as in Reference Example 11, N-α-naphthalenesulfonyl-(L)-isoleucyl-(L)-phenylalaninal was produced, which was recrystallized from ethyl acetate-hexane. m.p.138-139°C $[\alpha]_D$=-24.3° (c=0.60,DMSO)(20°C).

Reference Example 20

By substantially the same procedure as in Reference Example 11, N-benzyloxycarbonyl-(L)-alanyl-(L)-alanyl-(L)-phenylalaninal was produced. m.p.161-163°C $[\alpha]_D$=-42.1° (c=0.65,DMSO)(20°C).

Reference Example 21

A tetrahydrofuran solution (50 ml) of N-benzyloxycarbonyl-(L)-isoleucyl-(L)-tryptophan methylester (11.3 g) and 5% Pd-C (3.0 g) was stirred for 2 hours under hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (50 ml). To this solution were added, under ice-cooling, α-naphthalenesulfonyl chloride (5.8 g) and N,N-dimethylaminopyridine (3.2 g). The mixture was stirred for 3 hours under ice-cooling. The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The organic layer was washed with an aqueous solution of citric acid, water, an aqueous solution of $NaHCO_3$ and brine, successively, followed by drying ($MgSO_4$). The solvent was distilled off to leave a pale yellow oily product, which was crystallized from ethyl acetate-hexane to give N-α-naphthalenesulfonyl-(L)-isoleucyl-(L)-tryptophan methylester (9.8g, 77%), m.p.172-174°C. $[\alpha]_D$=+57.5° (c=0.20,$CHCl_3$)(20°C).

Reference Example 22

N-α-naphthalenesulfonyl-(L)-isoleucyl-(L)-tryptophan methylester (6.9 g) was dissolved in a mixture of tetrahydrofuran (THF) (40 ml) and methanol

(20 ml). To this solution was added dropwise an aqueous solution of potassium hydroxide (1.5 g) under ice-cooling. The mixture was stirred for 20 hours under ice-cooling. The reaction mixture was acidified with 1N-HCl. The organic solvent was distilled off under reduced pressure, and the residue was subjected to extraction with ethyl acetate. The organic layer was washed with brine and dried ($MgSO_4$). The solvent was distilled off, and the residual white solid was washed with ethyl acetate to give N-α-naphthalenesulfonyl-(L)-isoleucyl-(L)-tryptophan (6.6g, 98%), m.p.167-168°C. $[\alpha]_D$=+26.5° (c=0.51,DMSO)(20°C).

Reference Example 23

To a tetrahydrofuran (THF) solution (40 ml) of N-α-naphthalenesulfonyl-(L)-isoleucyl-(L)-tryptophan (4.0 g) and N-methylmorpholine (1.05 ml) was added, under ice-cooling, isobutyl chloroformate (1.25 ml). The mixture was stirred for 30 minutes under ice-cooling, then the salt formed as precipitate was filtered off and washed well with ether. The filtrate was cooled with ice, to which was added an ether solution of diazomethane. The mixture was stirred for one hour. Then, excess amount of diazomethane was distilled off, while introducing nitrogen gas. The reaction mixture was diluted with ethyl acetate. The ethyl acetate solution was washed with brine and dried ($MgSO_4$). The solvent was distilled off, and the residue was dissolved in methanol (40 ml). To this solution was added silver oxide (1.0 g), and the mixture was stirred for 30 minutes at 50°C. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (2:3), N-α-naphthalenesulfonyl-(L)-isoleucyl-(L)-β-homotryptophan methylester (2.45g, 58%) was produced.

$[\alpha]_D$=-18.1° (c=0.13,$CHCl_3$)(20°C).

^{1}H-NMR(δ ppm in $CDCl_3$): 0.5-0.9(7H,m), 1.0-1.3(1H,m), 1.5-1.8(1H,m), 2.23(2H,d,J=5.6Hz), 2.51(1H,dd,J=6.2 & 14.6Hz), 2.64(1H,dd,J=8.0 & 14.6Hz), 3.48(1H,dd,J=5.2 & 8.0Hz), 3.63(3H,s), 4.2-4.4(1H,m), 5.42(1H,d,J=8.2Hz), 6.35(1H,d,J=8.8Hz), 6.91(1H,d,J=2.2Hz), 7.1-7.8(7H,m), 7.90(1H,d,J=8.0Hz), 8.03(1H,d,J=8.4Hz), 8.09(1H,bs), 8.24(1H,d,J=7.0Hz), 8.69(1H,d,J=8.4Hz).

Reference Example 24

In a mixture of ethanol (50 ml) and tetrahydrofuran (50 ml) were dissolved N-α-naphthalenesulfonyl-(L)-isoleucyl-(L)-β-homotryptophan methylester (2.3 g) and sodium borohydride (1.5 g). To the solution was added lithium chloride (1.6 g) portionwise. The solution was stirred for 3 hours at room temperature, and for further 2 hours at 55°C, then the solvent was distilled off under reduced pressure. To the residue was added ethyl acetate. The mixture was washed with an aqueous solution of citric acid, water, an aqueous solution of $NaHCO_3$ and brine, followed by drying ($MgSO_4$). The solvent was distilled off. The residual pale yellow oily product was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (3:1), N-α-naphthalenesulfonyl-(L)-isoleucine (1S)-3-hydroxy-1-(3-indolylmethyl)-propylamide (1.5g, 68%) was obtained.

$[\alpha]_{Hg}$=-11.36° (c=0.42,$CHCl_3$)(20°C).

^{1}H-NMR(δ ppm in $CDCl_3$): 0.2-0.7(9H,m), 1.5-1.8(2H,m), 2.45(1H,dd,J=8.6 & 14.6Hz), 2.76(1H,dd,J=5.4 & 14.6Hz), 2.8-3.0(1H,m), 3.2-3.4(1H,m), 3.47(1H,dd,J=4.0 & 9.8Hz), 3.59(1H,dd,J=4.0 & 5.4Hz), 4.0-4.2(1H,m), 5.06(1H,d,J=7.4Hz), 6.16(1H,d,J=8.8Hz), 6.95(1H,d,J=2.2Hz), 7.1-7.4(3H,m), 7.5-7.8(4H,m), 7.98(1H,d,J=8.0Hz), 8.09(1H,d,J=8.2Hz), 8.20(1H,bs), 8.25(1H,dd,J=1.2, 7.2Hz), 8.70(1H,d,J=8.2Hz).

Reference Example 25

To a solution of N-b nzyloxycarbonyl-(L)-tyrosyl-(L)-tryptophanol (7.7 g) in methanol (50 ml)-tetrahydrofuran (50 ml) was added Pd-C (5%, 2.6 g). Catalytic hydrogenation was conducted at room temperature under one atomospheric pressure. The catalyst was filtered off, and the filtrate was concentrated to give an oily product. To a solution of this oily product and quinoline-2-carboxylic acid (2.9 g) in N,N-dimethylformamide (60 ml) were added 1-hydroxybenzotriazole (HOBt) (2.7 g) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (WSCD·HCl) (3.4 g) at 0°C. The reaction mixture was stirred for 18 hours at room temperature, which was poured into ice-water and subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with an aqueous solution of sodium hydrogencarbonate and water, successively, followed by drying ($MgSO_4$). The solvent was distilled off, and the residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate, N-(quinoline-2-carbonyl)-(L)-tyrosyl-(L)-tryptophanol(7.2 g, 89 %) was produced.

$[\alpha]_D$=-34.2° (c=0.386, CH_3OH).

NMR(δ ppm in d_6-DMSO):

2.5-3.5(6H,m), 3.9-4.1(1H,m), 4.7-4.9(1H,m), 6.60(2H,d,J=8.4Hz), 6.9-7.2(5H,m), 7.29(1H,d,J=7.8Hz), 7.61(1H,d,J=7.6Hz), 7.7-8.3(6H,m), 8.58(1H,d,J=8.6Hz), 8.70(1H,d,J=8.4Hz), 9.15(1H,br s), 10.77(1H,s).

Elemental Analysis

Calcd. for $C_{30}H_{28}N_4O_4 \cdot 1/2H_2O$

: C, 69.62; H, 5.65; N, 10.82

Found : C, 69.97; H, 5.85; N, 10.40

Reference Example 26

By substantially the same procedure as in Reference Example 25, N-(quinoline-2-carbonyl)-(L)-leucyl-(L)-tryptophanol was produced from N-

benzyloxycarbonyl-(L)-leucyl-(L)-tryptophanol.
$[\alpha]_D$=+16.6° (c=0.231, CH_3OH).
NMR(δ ppm in d_6-DMSO):
0.93(3H,d,J=6.0Hz), 0.95(3H,d,J=6.0Hz), 1.0-2.0(3H,m), 3.0(2H,d,J=7.0Hz), 2.9-3.1(1H,m), 3.6-3.9(2H,m), 4.2-4.4(1H,m), 4.6-4.8(1H,m), 6.70(1H,d,J=7.4Hz), 6.9-7.2(4H,m), 7.5-8.0(5H,m), 8.14(1H,d,J=8.4Hz), 8.19(1H,d,J=8.4Hz), 8.30(1H,d,J=8.8Hz), 8.48(1H,d,J=8.4Hz).
Elemental Analysis
Calcd. for $C_{27}H_{30}N_4O_3 \cdot 1/2H_2O$
: C, 69.36; H, 6.68; N, 11.98
Found : C, 69.57; H, 6.65; N, 12.00

Reference Example 27

By substantially the same procedure as in Reference Example 25, N-(pyridine-2-carbonyl)-(L)-isoleucyl-(L)-tryptophanol was produced from N-benzyloxycarbonyl-(L)-isoleucyl-(L)-tryptophanol.
$[\alpha]_D$=-26.5° (c=0.773, CH_3OH).
NMR(δ ppm in d_6-DMSO):
0.83(3H,d,J=7.6Hz), 0.85(3H,d,J=6.8Hz), 0.9-1.2(1H,m), 1.3-1.6(1H,m), 1.7-2.0(1H,m), 2.76(1H,dd,J=7.0&14.4Hz), 2.95(1H,dd,J=6.2&14.4Hz), 3.2-3.6(2H,m), 3.9-4.1(1H,m), 4.44(1H,dd,J=7.0&9.2Hz), 6.8-7.1(2H,m), 7.09(1H,d,J=1.6Hz), 7.28(1H,d,J=7.8Hz), 7.5-7.7(2H,m), 8.0-8.2(3H,m), 8.53(1H,d,J=9.2Hz), 8.68(1H,d,J=4.8Hz), 10.74(1H,br s).
Elemental Analysis
Calcd. for $C_{23}H_{28}N_4O_3 \cdot 1/4CH_3COOC_2H_5 \cdot 1/4H_2O$
: C, 66.26; H, 7.07; N, 12.88
Found : C, 66.26; H, 6.91; N, 12.80

Reference Example 28

To a solution of N-benzyloxycarbonyl-(L)-isoleucyl-(L)-tryptophanol (8.0 g) in methanol (50 ml)-tetrahydrofuran (50 ml) was added Pd-C (5 %, 2.5 g). Catalytic hydrogenation was conducted at room

temperature under one atomospheric pressure. The catalyst was filtered off, and the filtrate was concentrated to give an oily product. To a solution of this oily product and quinoline-8-sulfonyl chloride (4.37 g) in N,N-dimethylformamide (40 ml) was 4-dimethylaminopyridine (DMAP) (2.5 g) at 0°C. The reaction mixture was stirred for 3 hours at 0°C, which was poured into ice-water and subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with an aqueous solution of citric acid, an aqueous solution of sodium hydrogencarbonate and water, successively, followed by drying ($MgSO_4$). The solvent was distilled off, and the residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (4:1, v/v), N-(quinoline-8-sulfonyl)-(L)-isoleucyl-(L)-tryptophanol (8.3 g, 91 %) was produced.

$[\alpha]_D$=-49.6° (c=0.688, CH_3OH).

NMR(δ ppm in d_6-DMSO):

0.73(3H,d,J=7.4Hz), 0.75(3H,d,J=8.2Hz), 0.9-1.3(1H,m), 1.4-1.7(2H,m), 1.87(1H,dd,J=5.6&14.4Hz), 2.34(1H,dd,J=7.8&14.4Hz), 2.9-3.1(2H,m), 3.3-3.5(1H,m), 3.75(1H,dd,J=6.8&8.8Hz), 6.85(1H,d,J=1.6Hz), 6.9-7.4(5H,m), 7.5-7.7(3H,m), 8.16(1H,d,J=8.4Hz), 8.22(1H,d,J=7.2Hz), 8.40(1H,dd,J=1.6&8.4Hz), 9.06(1H,dd,J=1.6&4.2Hz), 10.71(1H,br s).

Elemental Analysis

Calcd. for $C_{26}H_{30}N_4O_4S \cdot 1/2CH_3COOC_2H_5 \cdot 1/2H_2O$

: C, 61.41; H, 6.44; N, 10.23

Found : C, 61.38; H, 6.33; N, 10.48

Reference Example 29

By substantially the same procedure as in Reference Example 11, N-(quinoline-2-carbonyl)-(L)-tyrosyl-(L)-tryptophanal was produced from N-(quinoline-2-carbonyl)-(L)-tyrosyl-(L)-tryptophanol.

$[\alpha]_D$=-68.3° (c=0.672, CH_3OH).

NMR(δ ppm in d_6-DMSO):
2.8-3.5(4H,m), 4.4-4.6(1H,m), 6.59(2H,d,J=6.8Hz), 6.9-8.8(15H,m), 9.16(1H,br s), 9.49(1H,s), 10.88(1H,s).
Elemental Analysis
Calcd. for $C_{30}H_{26}N_4O_4 \cdot 1/2CH_3COOC_2H_5$
: C, 69.80; H, 5.49; N, 10.18
Found : C, 69.71; H, 5.47; N, 10.18

Reference Example 30

By substantially the same procedure as in Reference Example 11, N-(quinoline-2-carbonyl)-(L)-leucyl-(L)-tryptophanal was produced from N-(quinoline-2-carbonyl)-(L)-leucyl-(L)-tryptophanol.
$[\alpha]_D$=-66.2° (c=0.602, CH_3OH).
NMR(δ ppm in $CDCl_3$):
0.95(3H,d,J=6.0Hz), 0.97(3H,d,J=6.0Hz), 1.6-2.0(3H,m), 3.22(1H,dd,J=7.8&15.0Hz), 3.33(1H,dd,J=8.2&15.0Hz), 4.7-5.0(2H,m), 6.9-7.2(5H,m), 7.5-7.9(4H,m), 8.0-8.3(4H,m), 8.53(1H,d,J=8.4Hz), 9.67(1H,s).

Reference Example 31

By substantially the same procedure as in Reference Example 11, N-(pyridine-2-carbonyl)-(L)-isoleucyl-(L)-tryptophanal was produced from N-(pyridine-2-carbonyl)-(L)-isoleucyl-(L)-tryptophanol.
$[\alpha]_D$=-26.9° (c=0.484, CH_3OH).
NMR(δ ppm in d_6-DMSO):
0.81(3H,t,J=7.2Hz), 0.86(3H,d,J=6.8Hz), 0.9-1.2(1H,m), 1.3-1.6(1H,m), 1.7-2.0(1H,m), 3.01(1H,dd,J=9.0&14.8Hz), 3.26(1H,dd,J=5.2&14.8Hz), 4.4-4.6(2H,m), 6.8-7.1(2H,m), 7.16(1H,d,J=1.0Hz), 7.31(1H,d,J=7.8Hz), 7.52(1H,d,7.8Hz), 7.6-7.7(1H,m), 7.9-8.2(3H,m), 8.52(1H,d,J=9.6Hz), 8.6-8.8(2H,m), 9.53(1H,s), 10.84(1H,br s).
Elemental Analysis
Calcd. for $C_{23}H_{26}N_4O_3 \cdot 1/2CH_3COOC_2H_5 \cdot 1/2H_2O$
: C, 65.34; H, 6.80; N, 12.19
Found : C, 65.56; H, 6.69; N, 12.54

Reference Example 32

By substantially the same procedure as in Reference Example 11, N-(quinoline-8-sulfonyl)-(L)-isoleucyl-(L)-tryptophanal was produced from N-(quinoline-8-sulfonyl)-(L)-isoleucyl-(L)-tryptophanol.

$[\alpha]_D$=+43.9° (c=0.473, CH_3OH).

NMR(δ ppm in d_6-DMSO):

0.73(3H,d,J=7.0Hz), 0.75(3H,d,J=6.8Hz), 0.9-1.2(1H,m), 1.3-1.7(2H,m), 2.53(1H,dd,J=8.2&15.0Hz), 2.80(1H,dd,J=6.2&15.0Hz), 3.7-3.9(1H,m), 3.89(1H,dd,J=6.2&9.0Hz), 6.9-7.7(8H,m), 8.1-8.4(3H,m), 8.45(1H,dd,J=1.6&8.2Hz), 8.81(1H,s), 8.98(1H,dd,J=1.6&4.2Hz), 10.87(1H,br s).

Elemental Analysis

Calcd. for $C_{26}H_{28}N_4O_4S \cdot 1/2CH_3COOC_2H_5 \cdot 1/2H_2O$

: C, 61.63; H, 6.10; N, 10.27

Found : C, 61.63; H, 6.08; N, 10.34

Working Example 1

N-t-Butoxycarbonyl-(L)-phenylalanyl-(L)-tryptophanal (2.4 g) and formylmethylene triphenylphosphorane (1.76 g) were dissolved in a mixture of tetrahydrofuran (THF) (10 ml) and toluene (30 ml). The solution was stirred for 15 hours at 50°C. The solvent was distilled off, and the residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (1:1), N-t-butoxycarbonyl-(L)-phenylalanine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide (2.2g, 86%) was obtained as a pale yellow powdery product.

$[\alpha]_D$=+6.0° (c=0.91,MeOH)(20°C).

^{1}H-NMR(δ ppm in $CDCl_3$): 1.35(9H,s), 2.9-3.1(4H,m), 4.2-4.4(1H,m), 4.8-5.1(2H,m), 5.85(1H,dd,J=7.6 & 15.6Hz), 6.14(1H,d,J=7.8Hz), 6.52(1H,dd,J=4.8 & 15.6Hz), 6.92(1H,d,J=2.0Hz), 7.0-7.4(9H,m), 8.22(1H,brs), 9.41(1H,d,J=7.8Hz).

Elemental Analysis

Calcd. for $C_{29}H_{31}N_3O_4S \cdot 1/2H_2O$
: C, 66.14; H, 6.12; N, 7.98
Found : C, 66.31; H, 6.02; N, 7.79

Working Example 2

By substantially the same procedure as in Working Example 1, N-α-naphthalenesulfonyl-(L)-isoleucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide was obtained as a pale yellow powdery product.
$[\alpha]_D$=-51.7° (c=0.25,$CHCl_3$)(20°C).
^{1}H-NMR(δ ppm in $CDCl_3$): 0.44(3H,d,J=6.8Hz), 0.5-0.9(5H,m), 1.6-1.8(1H,m), 2.72(1H,dd,J=7.8 & 14.8Hz), 2.90(1H,dd,J=6.2 & 14.8Hz), 3.54(1H,dd,J=4.6 & 7.6Hz), 4.7-4.9(1H,m), 5.13(1H,d,J=7.6Hz), 5.88(1H,dd,J=7.8 & 15.8Hz), 6.35(1H,d,J=8.8Hz), 6.43(1H,dd,J=5.0 & 15.8Hz), 7.01(1H,d,J=2.2Hz), 7.1-7.3(2H,m), 7.38(1H,d,J=7.8Hz), 7.4-7.8(4H,m), 7.95(1H,d,J=8.0Hz), 8.08(1H,d,J=8.0Hz), 8.22(1H,brs), 8.25(1H,d,J=7.4Hz), 8.67(1H,d,J=8.4Hz), 9.40(1H,d,J=7.6Hz).

Working Example 3

By substantially the same procedure as in Working Example 1, N-α-naphthalenesulfonyl-(L)-isoleucine (1S)-3-formyl-1-methyl-2-propenylamide was obtained as a pale yellow crystalline product, m.p.182-183°C.
$[\alpha]_D$=-63.9° (c=0.64,$CHCl_3$)(20°C).

Working Example 4

By substantially the same procedure as in Working Example 1, N-α-naphthalenesulfonyl-(L)-isoleucine (1S)-3-formyl-1-benzyl-2-propenylamide was obtained as a pale yellow crystalline product, m.p.165-167°C.
$[\alpha]_D$=-70.3° (c=0.50,$CHCl_3$)(20°C).

Working Example 5

By substantially the same procedure as in Working Example 1, N-valproyl-(L)-valine (1S)-3-formyl-1-(3-indolylmethyl)-2-prop nylamide was obtained as a pale yellow crystalline product, m.p.208-209°C.
$[\alpha]_D$=-24.6° (c=0.39,MeOH)(20°C).

Working Example 6

By substantially the same procedure as in Working Example 1, N-β-naphthalenesulfonyl-(L)-isoleucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide was obtained.

$[\alpha]_D$=-43.6° (c=0.25,MeOH)(20°C).

^{1}H-NMR(δ ppm in $CDCl_3$): 0.5-0.9(7H,m), 1.0-1.2(1H,m), 1.6-1.9(1H,m), 2.87(2H,d,J=6.6Hz), 3.64(1H,dd,J=4.6 & 7.6Hz), 4.8-5.0(1H,m), 5.34(1H,d,J=7.6Hz), 6.10(1H,dd,J=7.6 & 16.0Hz), 6.48(1H,dd,J=4.8 & 16.0Hz), 6.51(1H,d,J=8.8Hz), 6.94(1H,d,J=2.2Hz), 7.1-8.0(10H,m), 8.29(1H,brs), 8.40(1H,s), 9.23(1H,d,J=7.4Hz).

Working Example 7

By substantially the same procedure as in Working Example 1, N-α-naphthalenecarbamoyl-(L)-isoleucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide was obtained as a pale yellow crystalline product, m.p.214-216°C(decomp.). $[\alpha]_D$=+32.4° (c=0.90,DMSO)(20°C).

Working Example 8

By substantially the same procedure as in Working Example 1, N-benzyloxycarbonyl-(L)-leucyl-(L)-leucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide was obtained as a pale yellow powdery product.

$[\alpha]_D$=-23.1° (c=0.73,MeOH)(20°C).

^{1}H-NMR(δ ppm in $CDCl_3$): 0.7-1.0(12H,m), 1.3-1.8(6H,m), 3.08(2H,d,J=7.0Hz), 4.0-4.2(1H,m), 4.3-4.5(1H,m), 5.07(2H,ABq,J=7.4 & 11.8Hz), 5.0-5.1(1H,m), 5.27(1H,brd,J=6.4Hz), 6.15(1H,dd,J=7.6 & 17.0Hz), 6.50(1H,brd,J=8.0Hz), 6.79(1H,dd,J=5.2 & 15.8Hz), 6.93(1H,brd,J=8.0Hz), 7.01(1H,d,J=2.4Hz), 7.0-7.4(3H,m), 7.32(5H,s), 7.54(1H,d,J=8.0Hz), 8.36(1H,brs), 9.44(1H,d,J=7.8Hz).

Working Example 9

By substantially the same procedure as in Working Example 1, N-b nzyloxycarbonyl-(L)-alanyl-(L)-alanine (1S)-3-formyl-1-benzyl-2-propenylamide was obtained as

a pale yellow crystalline product, m.p.154-155°C.
$[\alpha]_D$=-42.2° (c=0.45,MeOH)(20°C).

Working Example 10

To a solution of N-α-naphthalenesulfonyl-(L)-isoleucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide (1.0 g) in tetrahydrofuran (THF) (20 ml) was added Pd-C (10%,0.40 g). Catalytic hydrogenation was conducted at room temperature under one atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to leave an oily product, which was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (2:1), N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-(3-indolylmethyl)propylamide (0.70g, 69%) was obtained.
$[\alpha]_D$=-14.3° (c=0.25,$CHCl_3$)(20°C).
^{1}H-NMR(δ ppm in $CDCl_3$): 0.4-1.1(9H,m), 1.6-1.8(2H,m), 1.9-2.3(2H,m), 2.49(1H,dd,J=6.8 & 14.4Hz), 2.62(1H,dd,J=6.4 & 14.4Hz), 3.55(1H,dd,J=4.6 & 7.8Hz), 3.9-4.1(1H,m), 5.40(1H,d,J=8.0Hz), 6.08(1H,d,J=9.0Hz), 6.92(1H,d,J=2.2Hz), 7.1-7.7(7H,m), 7.91(1H,d,J=8.0Hz), 8.03(1H,d,J=8.0Hz), 8.24(1H,d,J=7.2Hz), 8.31(1H,brs), 8.68(1H,d,J=8.4Hz), 9.58(1H,s).
Elemental Analysis
Calcd. for $C_{29}H_{33}N_3O_4S \cdot 1/2H_2O$
: C, 65.89; H, 6.48; N, 7.95
Found : C, 65.88; H, 6.41; N, 7.68

Working Example 11

N-(2-Benzyl-3-phenylpropionyl)-(L)-tryptophanal (11.5 g) and (formylmethylene)triphenylphosphorane (8.5 g) were dissolved in a mixture of tetrahydrofuran (THF)(10 ml) and toluene (100 ml). The solution was stirred for 13 hours at 55°C. The solvent was distilled off, and the residue was subjected to a silica gel column chromatography. From th fracti n eluted with thyl acetate-hexane (1:2), a pale brown

powdery product was obtained. This powdery product was dissolved in ethanol, to which was added Pd-C (10%, 2.0 g). The mixture was subjected to catalytic hydrogenation reduction at room temperature under one atmospheric pressure. The Pd-C was filtered off, and the filtrate was concentrated under reduced pressure to leave an oily product. This oily product was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (1:2), N-[(1R)-3-formyl-1-(3-indolylmethyl)propyl]-2-benzyl-3-phenylpropionamide (0.45g, 5%) was obtained, which was recrystallized from ethyl acetate-hexane.
m.p.180-181°C. $[\alpha]_D$=+22.0° (c=0.36,$CHCl_3$)(20°C).
Elemental Analysis
Calcd. for $C_{29}H_{30}N_2O_2 \cdot 1/4H_2O$
: C, 78.61; H, 6.94; N, 6.32
Found : C, 78.88; H, 6.77; N, 6.24

Working Example 12

By substantially the same procedure as in Working Example 10, N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-methylpropylamide was produced,
m.p.160-161°C. $[\alpha]_D$=-27.4° (c=0.29,$CHCl_3$) (20°C).

Working Example 13

By substantially the same procedure as in Working Example 10, N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-benzylpropylamide was obtained as a pale yellow powdery product.
$[\alpha]_D$=-32.4° (c=0.50,$CHCl_3$)(20°C).
^{1}H-NMR(δ ppm in $CDCl_3$): 0.4-1.2(8H,m), 1.4-1.9(3H,m), 1.9-2.4(3H,m), 2.55(1H,dd,J=6.1 & 14Hz), 3.49(1H,dd,J=4.1 & 6.9Hz), 3.8-4.0(1H,m), 4.94(1H,d,J=7.0Hz), 5.92(1H,d,J=9.6Hz), 6.9-7.1(2H,m), 7.1-7.3(3H,m), 7.5-7.9(3H,m), 7.98(1H,d,J=8.2Hz), 8.09(1H,d,J=8.2Hz), 8.26(1H,dd,J=1.2 & 7.4Hz), 8.68(1H,d,J=8.8Hz), 9.64(1H,s).

Working Example 14

By substantially the same procedure as in Working Example 10, N-valproyl-(L)-valine (1R)-3-formyl-1-(3-indolylmethyl)propylamide, m.p.173-174°C, was produced. m.p. 173-174°C. $[\alpha]_D$=-7.0° (c=0.58,MeOH)(20°C).

Working Example 15

By substantially the same procedure as in Working Example 10, N-β-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-(3-indolylmethyl)propylamide, m.p.175-177°C, was produced. $[\alpha]_D$=-18.4° (c=0.65,MeOH)(20°C).

Working Example 16

By substantially the same procedure as in Working Example 10, N-t-butoxycarbonyl-(L)-phenylalanine (1R)-3-formyl-1-(3-indolylmethyl)propylamide, m.p.97-98°C was produced. $[\alpha]_D$=-3.5° (c=0.69,MeOH)(20°C).

Working Example 17

By substantially the same procedure as in Working Example 10, N-α-naphthalenecarbamoyl-(L)-isoleucine (1R)-3-formyl-1-(3-indolylmethyl)propylamide, m.p.221-222°C, was produced. $[\alpha]_D$=+20.6° (c=0.74,DMSO)(20°C).

Working Example 18

To a solution of N-benzyloxycarbonyl-(L)-leucyl-(L)-leucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide (1.0 g) and acetic anhydride (0.18 ml) in a mixture of methanol (15 ml) and tetrahydrofuran (THF) (15 ml) was added Pd-C (10%,0.5 g). The mixture was subjected to catalytic hydrogenation under one atmospheric pressure at room temperature. The Pd-C was filtered off, and the filtrate was concentrated under reduced pressure to leave an oily product. This oily product was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (4:1), N-acetyl-(L)-leucyl-(L)-leucine (1R)-3-formyl-1-(3-indolylmethyl)propylamide, m.p.168-170°C was produced. $[\alpha]_D$=-48.0° (c=0.45,MeOH)(20°C).

Working Example 19

N-α-naphthalenesulfonyl-(L)-isoleucine (1S)-3-

hydroxy-1-(3-indolylm thyl)propylamide (0.50 g) and triethylamine (0.41 ml) were dissolved in a mixture of dimethyl sulfoxide (2 ml) and dichloromethane (6 ml). To this solution was added, under ice-cooling, a dimethyl sulfoxide solution (2 ml) of a sulfur trioxide·pyridine complex (0.47 g). The mixture was stirred for 3 hours under ice-cooling. The reaction mixture was poured into an aqueous solution of citric acid, which was subjected to extraction with ethyl acetate. The organic layer was washed with brine, followed by drying ($MgSO_4$). The solvent was distilled off, and the residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (1:1), was obtained N-α-naphthalenesulfonyl-(L)-isoleucine (1S)-2-formyl-1-(3-indolylmethyl)ethylamide (0.35g, 70%).

$[\alpha]_D$=-38.7° (c=0.19,MeOH)(20°C).

^{1}H-NMR(δ ppm in $CDCl_3$): 0.5-0.9(7H,m), 1.0-1.2(1H,m), 1.6-1.8(1H,m), 2.12(1H,dd,J=7.0 & 17.4Hz), 2.28(1H,dd,J=5.4 & 17.4Hz), 2.57(1H,dd,J=6.6 & 14.6Hz), 2.68(1H,dd,J=7.6 & 14.6Hz), 3.53(1H,dd,J=5.6 & 8.0Hz), 4.3-4.5(1H,m), 5.73(1H,d,J=8.0Hz), 6.36(1H,d,J=8.4Hz), 6.91(1H,d,J=2.0Hz), 7.0-7.7(7H,m), 7.89(1H,d,J=8.0Hz), 8.01(1H,d,J=8.0Hz), 8.22(1H,d,J=7.2Hz), 8.46(1H,bs), 8.69(1H,d,J=8.4Hz), 9.37(1H,s).

Working Example 20

N-α-naphthalenesulfonyl-(L)-isoleucine (1S)-2-formyl-1-(3-indolylmethyl)ethylamide (0.84 g) and (formylmethylene)triphenylphosphorane (0.61 g) were dissolved in a mixture of tetrahydrofuran (4 ml) and benzene (20 ml). The solution was stirred for 15 hours at 60°C. The solvent was distilled off under reduced pressure. The residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (3:2), was produced N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-4-formyl-1-(3-

indolylmethyl)-3-butenylamide (0.49g, 55%).
$[\alpha]_D$=-43.7° (c=0.24,MeOH)(20°C).
^{1}H-NMR(δ ppm in $CDCl_3$): 0.4-0.7(7H,m), 0.8-1.0(1H,m), 1.6-1.8(1H,m), 1.9-2.1(1H,m), 2.2-2.4(1H,m), 2.63(1H,dd,J=6.8 & 14.6Hz), 2.73(1H,dd,J=6.0 & 14.6Hz), 3.49(1H,dd,J=4.6 & 7.8Hz), 4.1-4.4(1H,m), 5.25(1H,d,J=7.8Hz), 5.97(1H<dd,J=6.6 & 15.8Hz), 6.12(1H,d,J=9.2Hz), 6.53(1H,dt,J=6.0 & 15.8Hz), 6.98(1H,d,J=1.8Hz), 7.1-7.3(3H,m), 7.37(1H,d,J=8.0Hz), 7.4-7.7(4H,m), 7.94(1H,d,J=8.2Hz), 8.06(1H,d,J=8.2Hz), 8.21(1H,bs), 8.23(1H,d,J=7.2Hz), 8.65(1H,d,J=8.6Hz), 9.37(1H,d,J=7.8Hz).

Working Example 21

N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-4-formyl-1-(3-indolylmethyl)-3-butenylamide (0.42 g) and 5%-palladium carbon (0.30 g) were added to tetrahydrofuran (15 ml). The mixture was hydrogenated under hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated. The residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (3:2), was obtained N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-4-formyl-1-(3-indolylmethyl)butylamide (0.37g, 87%).
$[\alpha]_D$=-21.3° (c=0.19,MeOH)(20°C).
^{1}H-NMR(δ ppm in $CDCl_3$): 0.5-0.7(7H,m), 0.8-1.0(2H,m), 1.2-1.5(3H,m), 1.6-1.8(1H,m), 2.1-2.3(2H,m), 2.48(1H,dd,J=6.8 & 14.6Hz), 2.61(1H<dd,J=6.2 & 14.6Hz), 3.55(1H,dd,J=4.4 & 8.0Hz), 3.9-4.1(1H,m), 5.37(1H,d,J=8.0Hz), 5.96(1H,d,J=8.8Hz), 6.91(1H,d,J=2.2Hz), 7.1-7.7(7H,m), 7.91(1H,d,J=7.8Hz), 8.03(1H,d,J=8.2Hz), 8.23(1H,d,J=7.6Hz), 8.24(1H,bs), 8.66(1H,d,J=8.2Hz), 9.62(1H,t,J=1.4Hz).

Working Example 22

By substantially the same procedure as in Example 1, N-(quinoline-2-carbonyl)-(L)-tyrosin (1S)-3-formyl-

1-(3-indolylmethyl)-2-propenylamide was produced by reacting N-(quinoline-2-carbonyl)-(L)-tyrosyl-(L)-tryptophanal with (formylmethylene)triphenyl-phosphorane.

$[\alpha]_D$=+8.4° (c=0.439, CH_3OH).

NMR(δ ppm in $CDCl_3$):

3.00(2H,d,J=6.4Hz), 3.02(1H,dd,J=9.0&13.4Hz), 3.20(1H,dd,J=5.4&13.4Hz), 4.7-4.9(1H,m), 4.9-5.1(1H,m), 5.80(1H,ddd,J=1.6&7.8&16.0Hz), 6.29(1H,d,J=8.0Hz), 6.61(1H,dd,J=5.4&16.0Hz), 6.7-8.3(16H,m), 8.42(1H,br s), 8.80(1H,d,J=8.0Hz), 9.37(1H,d,J=7.8Hz).

Working Example 23

By substantially the same procedure as in Example 10, N-(quinoline-2-carbonyl)-(L)-tyrosine (1R)-3-formyl-1-(3-indolylmethyl)propylamide was produced by subjecting N-(quinoline-2-carbonyl)-(L)-tyrosine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide to catalytic hydrogenation.

$[\alpha]_D$=-13.1° (c=0.618, CH_3OH).

NMR(δ ppm in $CDCl_3$):

1.3-2.4(4H,m), 2.7-3.3(4H,m), 4.0-4.3(1H,m), 4.6-4.8(1H,m), 5.95(1H,d,J=8.8Hz), 6.7-8.4(17H,m), 8.78(1H,d,J=8.4Hz), 9.55(1H,s).

Working Example 24

By substantially the same procedure as in Example 1, N-(quinoline-2-carbonyl)-(L)-leucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide was produced by reacting N-(quinoline-2-carbonyl)-(L)-leucyl-(L)-tryptophanal with (formylmethylene)triphenyl-phosphorane.

$[\alpha]_D$=+30.4° (c=0.514, CH_3OH).

NMR(δ ppm in $CDCl_3$):

0.94(3H,d,J=5.6Hz), 0.97(3H,d,J=5.6Hz), 1.6-2.0(3H,m), 3.09(2H,d,J=6.6Hz), 4.7-4.9(1H,m), 5.0-5.3(1H,m), 6.22(1H,ddd,J=1.6&7.8&15.8Hz), 6.87(1H,ddd,J=4.8&7.8Hz), 6.9-7.1(5H,m), 7.4-7.9(4H,m),

7.98(1H,br s), 8.10(1H,d,J=8.6Hz), 8.14(1H,d,J=7.6Hz), 8.25(1H,d,J=8.6Hz), 8.49(1H,d,J=8.6Hz), 9.51(1H,d,J=7.6Hz).

Elemental Analysis

Calcd. for $C_{29}H_{30}N_4O_3 \cdot 1/2CH_3COOC_2H_5 \cdot 1/4H_2O$

: C, 70.10; H, 6.55; N, 10.55

Found : C, 70.14; H, 6.48; N, 10.80

Working Example 25

By substantially the same procedure as in Example 1, N-(pyridine-2-carbonyl)-(L)-isoleucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide was produced by reacting N-(pyridine-2-carbonyl)-(L)-isoleucyl-(L)-tryptophanal with (formylmethylene)triphenyl-phosphorane.

$[\alpha]_D$=-4.9° (c=0.486, CH_3OH).

NMR(δ ppm in $CDCl_3$):

0.88(3H,t,J=7.4Hz), 0.96(3H,d,J=6.8Hz), 1.0-1.3(1H,m), 1.4-1.6(1H,m), 2.0-2.2(1H,m), 3.08(2H,d,J=7.4Hz), 4.56(1H,dd,J=6.6&9.2Hz), 5.1-5.3(1H,m), 6.20(1H,ddd,J=1.4&7.8&15.8Hz), 6.8-7.8(9H,m), 7.99(1H,dd,J=1.0&7.6Hz), 8.16(1H,br s), 8.48(1H,d,J=9.2Hz), 8.57(1H,dd,J=1.4&4.2Hz), 9.49(1H,d,J=7.6Hz).

Elemental Analysis

Calcd. for $C_{25}H_{28}N_4O_3 \cdot 1/4CH_3COOC_2H_5 \cdot 1/4H_2O$

: C, 68.03; H, 6.70; N, 12.20

Found : C, 68.10; H, 6.67; N, 11.92

Working Example 26

By substantially the same procedure as in Example 1, N-(quinoline-8-sulfonyl)-(L)-isoleucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide was produced by reacting N-(quinoline-8-sulfonyl)-(L)-isoleucyl-(L)-tryptophanal with (formylmethylene)triphenyl-phosphorane.

$[\alpha]_D$=+57.0° (c=0.173, CH_3OH).

NMR(δ ppm in $CDCl_3$):

0.34(3H,d,J=7.0Hz), 0.51(3H,t,J=6.8Hz), 0.6-1.2(2H,m), 1.5-1.8(1H,m), 2.92(1H,dd,J=7.2&14.4Hz), 3.04(1H,dd,J=7.0&14.4Hz), 3.64(1H,dd,J=4.4&5.6Hz), 4.8-5.0(1H,m), 6.21(1H,ddd,J=1.6&7.6&15.8Hz), 6.52(1H,d,J=5.6Hz), 6.73(1H,dd,J=8.4&15.8Hz), 6.88(1H,d,J=8.0Hz), 7.1-7.7(7H,m), 8.04(1H,dd,J=1.6&7.2Hz), 8.2-8.4(3H,m), 9.04(1H,dd,J=1.6&4.2Hz), 9.46(1H,d,J=7.6Hz).

Elemental Analysis

Calcd. for $C_{28}H_{30}N_4O_4S \cdot H_2O$

: C, 62.67; H, 6.01; N, 10.44

Found : C, 62.77; H, 5.77; N, 10.16

Working Example 27

By substantially the same procedure as in Example 10, N-(quinoline-8-sulfonyl)-(L)-isoleucine (1R)-3-formyl-1-(3-indolylmethyl)propylamide was produced by subjecting N-(quinoline-8-sulfonyl)-(L)-isoleucine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide to catalytic hydrogenation.

$[\alpha]_D$=+70.5° (c=0.347, CH_3OH).

NMR(δ ppm in $CDCl_3$):

0.39(3H,d,J=7.0Hz), 0.52(3H,t,J=7.2Hz), 0.7-2.0(2H,m), 2.46(2H,t,J=7.4Hz), 2.67(2H,d,J=6.6Hz), 3.5-3.7(1H,m), 4.0-4.2(1H,m), 6.51(1H,d,J=8.8Hz), 6.58(1H,d,J=5.8Hz), 6.99(1H,d,J=2.0Hz), 7.1-7.7(6H,m), 8.02(1H,d,J=7.8Hz), 8.24(1H,dd,J=1.6&8.4Hz), 8.36(1H,d,J=7.4Hz), 8.38(1H,br s), 9.03(1H,dd,J=1.0&4.2Hz), 9.69(1H,s).

Elemental Analysis

Calcd. for $C_{28}H_{32}N_4O_4S \cdot 1/2H_2O$

: C, 63.50; H, 6.28; N, 10.58

Found : C, 63.37; H, 6.39; N, 10.38

Preparation Examples

A prophylactic or therapeutic apent of the present invention can, for example, be produced with the following formulations:

1. Capsule

(1)	Compound obtained in Example 8	10 mg
(2)	Lactose	90 mg
(3)	Micronized cellulose	70 mg
(4)	Magnesium stearate	10 mg
	Total	180 mg per capsule

Components (1), (2) and (3) and a half portion of component (4) are mixed and granulated. To these granules, the remaining portion of component (4) is added, and the whole mixture is packed in a gelatin capsule.

2. Tablet

(1)	Compound obtained in Example 10	10 mg
(2)	Lactose	35 mg
(3)	Corn starch	150 mg
(4)	Micronized cellulose	30 mg
(5)	Magnesium stearate	5 mg
	Total	230 mg per tablet

Components (1), (2) and (3), a two-third portion of component (4) and a half portion of component (5) are mixed and granulated. To these granules, the remaining portions of components (4) and (5) are added, and the whole mixture is tableted by compressive tableting.

Industrial Applicability

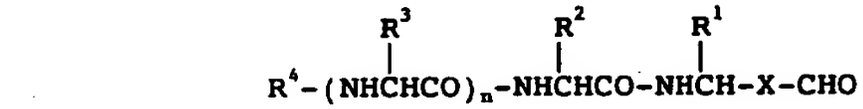
Since the compounds (Ia) and (I) of this invention have a strong action of inhibiting cysteine protease, they are useful as medicines for prophylaxis and treatment of bone diseases and various diseases caused by abnormal exasperation of cysteine protease.

CLAIMS

1. A compound of the formula (Ia'):

wherein Q' stands for one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; and X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety, or a salt thereof.

2. A compound claimed in Claim 1, in which is one represented by the formula (I'):



wherein R^1, R^2 and R^3 independently stand for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety; and n is 0 or 1, or a salt thereof.

3. A compound claimed in Claim 2, in which R^1, R^2 and R^3 are independently an optionally substituted alkyl group.

4. A compound claimed in Claim 2, in which R^1, R^2 and R^3 are indep ndently a straight-chain or branched C_{1-6} alkyl group which may b substituted with an optionally substituted aryl group or a heterocyclic group.

5. A compound claimed in Claim 4, in which the aryl group is a phenyl group.

6. A compound claimed in Claim 4, in which the heterocyclic group is an aromatic heterocyclic group.

7. A compound claimed in Claim 2, in which R^1 is a straight-chain or branched C_{1-6} alkyl group which is substituted with an aryl group or a heterocyclic group.

8. A compound claimed in Claim 2, in which R^2 and R^3 are independently a straight-chain or branched C_{1-6} alkyl group.

9. A compound claimed in Claim 2, in which the acyl group is that derived from a carboxylic acid, sulfonic acid, sulfinic acid, carbamic acid or thiocarbamic acid.

10. A compound claimed in Claim 2, in which the acyl group is represented by the formula $-SO_2R^6$ or $-COR^9$, wherein R^6 and R^9 are independently a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group.

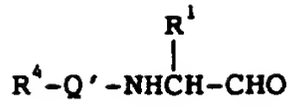
11. A compound claimed in Claim 2, in which the optionally esterified carboxyl group is represented by the formula $-COOR^5$ wherein R^5 is a C_{1-6} alkyl, a C_{2-6} alkenyl or a C_{6-10} aralkyl.

12. A compound claimed in Claim 2, in which n is 1.

13. A compound claimed in Claim 2, in which n is 0.

14. A compound claimed in Claim 2, which is N-valproyl-(L)-valine (1S)-3-formyl-1-(3-indolylmethyl)-2-propenylamide, N-benzyloxycarbonyl-(L)-alanyl-(L)-alanine (1S)-3-formyl-1-benzyl-2-propenylamide, N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-(3-indolylmethyl)propylamide or N-α-naphthalenesulfonyl-(L)-isoleucine (1R)-3-formyl-1-benzylpropylamide.

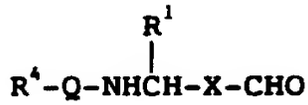
15. A method of producing a compound of Claim 1 which comprises reacting a compound of the formula:



wherein Q' stands for one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; and R^4 stands for an optionally esterified carboxyl group or an acyl group, or a salt thereof, with an acetaldehyde derivative, followed by reduction upon necessity.

16. A composition which comprises a compound of Claim 1.

17. A composition which comprises a compound of the formula (Ia):

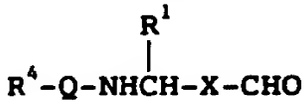


wherein Q stands for a direct bond or one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; and X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety, or a pharmaceutically acceptable salt thereof.

18. A composition claimed in Claim 17, which is for inhibiting a cysteine protease.

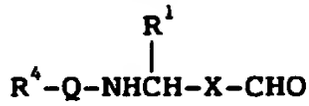
19. A composition claimed in Claim 17, which is for the prevention or treatment of a bone disease.

20. A method for preventing or treating a bone disease in a mammal which comprises administering to said mammal a pharmaceutically effective amount of a compound of the formula (Ia):



wherein Q stands for a direct bond or one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; and X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety, or a pharmaceutically acceptable salt thereof.

21. Use of a compound of the formula (Ia):



wherein Q stands for a direct bond or one or two amino acid residual groups which may be substituted; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R^4 stands for an optionally esterified carboxyl group or an acyl group; and X stands for an optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to be used as a cysteine protease inhibitor.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/JP 95/01933

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/16 A61K31/40 A61K31/435 A61K38/05 C07D401/12
C07C311/19 C07K5/062

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 116, no. 12, 30 March 1992 Columbus, Ohio, US; abstract no. 129662k, TANAMI,TORU ET AL. 'Preparation of tripeptide aldehyde derivatives as cysteine protease inhibitors' * RN 139519-17-8 * see abstract & JP,A,91 258 800 (TAISHO PHARMACEUTICAL CO.,LTD.) ---	1,2,18
X	EP,A,0 128 762 (SANKYO COMPANY LTD.) 19 December 1984 example 6 and 17 * --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1995	16. 01. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/JP 95/01933

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 611 756 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 24 August 1994 cited in the application see claims	1,18

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 95/01933

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 20 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.